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VOL. CLXIX, No. 1 JANUARY, 1925 No. 634

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ESTABLISHED 1820

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JANUARY, 1925

ORIGINAL ARTICLES.

INJURIES TO THE MUSCULOSPIRAL NERVE.

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The musculospiral nerve is frequently involved in injuries of the upper extremity, due largely to the close approximation of the nerve to the shaft of the humerus in its middle third. von Busch,[10] in 1863, was the first to describe the paralysis resulting from injury of the musculospiral nerve in fractures of the humerus. Since his discovery many attempts have been made to restore the anatomical continuity of the nerve. In the World War, operative procedures were used with an appreciable measure of success in cases of paralysis of the musculospiral nerve resulting from wounds or fractures.

Slight injuries to the musculospiral nerve are frequently overlooked, especially as the paralytic symptoms may disappear rapidly after reduction of the fracture. In some cases, however, paralysis follows injury to the nerve trunk, due to the original trauma or to subsequent pressure upon the nerve from bony callus or scar tissue. These injuries demand early recognition and treatment, for such damage unrecognized often leads to a serious loss of function.

Very little has appeared in American literature on this important subject. It is our purpose to review the literature, particularly that of foreign countries, and to present our personal experiences with several of the more severe types of these injuries.

Anatomy of the Nerve. The musculospiral nerve is the principal continuation of the posterior cord of the brachialis plexus, and the only branch prolonged into the arm. It arises behind the axillary vessels, turns backward with the superior profunda artery between the long and internal heads of the triceps, and runs beneath the external head of the muscle in the musculospiral groove of the humerus, to the outer side of the arm. It pierces the external intermuscular septum, and descends between the brachialis anticus and the supinator longus to the front of the external condyle, where it divides into the radial and posterior interosseous nerves. The radial is a cutaneous nerve, supplying the outer side of the thumb and the skin of two and a half fingers. The posterior interosseous supplies all the muscles on the back of the forearm except the anconeus.

The branches of the musculospiral nerve, arising on the inner side of the humerus, consist of the muscular branches supplying the long and inner heads of the triceps, and the internal cutaneous branch which passes backward beneath the intercosto-humeral nerve and supplies filaments to the skin over the long head of the triceps. The posterior branches of the musculospiral nerve consist of a fasciculus of muscular branches which supply the outer and inner heads of the triceps muscle and the anconeus. The external branches consist of the external cutaneous branches and the muscular branches. The external cutaneous branches distribute filaments to the lower half of the arm on its outer and anterior aspect and the branch descending to the wrist distributes offsets to the lower half of the arm and forearm, on their posterior aspect. The muscular branches supply the supinator longus, the extensor carpi radialis longior and frequently a small branch to the outer part of the brachialis anticus (Quain[63]).

Symptoms. The symptoms of injury to the musculospiral nerve vary in degree and duration according to the severity of the trauma and the resultant pathology. If, in a fracture of the humerus, the pressure on, or the stretching of the nerve is slight, any symptoms traceable to nerve injury may disappear in a few minutes. If continuity is interfered with, certain motor and sensory changes make their appearance.

Motor Changes. The wrist drops and the power of extension of the hand is lost. The hand is held pronated and half-flexed with the palmar surface slightly concave. If the hand is placed on a resistant surface, the lateral movements are impossible. If this deformity has existed for some time, there is a marked prominence on the dorsum of the hand, due to the stretching of the dorsal ligament of the wrist and the subluxation of the carpus. Extension of the fingers at the metacarpophalangeal joints as well as extension of the terminal phalanx of the thumb is lost.

The forearm is half-flexed and no extension is possible at the elbow.

Supination is entirely lost when the forearm is extended on the arm, but if the forearm is flexed, a moderate degree of supination is possible through the action of the biceps.

Sensory Changes. There may or may not be any loss of sensibility. The area of loss when the nerve is divided extends roughly over the dorsum of the hand and lower wrist. There is no loss of sensibility in the forearm beyond a slight impairment of a very small area to the faradic current, and even this is doubtful.

Several theories have been expounded to explain the slight changes in sensibility. Létiévant[45] attributes it either to the abundant anastomoses between the median and ulnar nerves which undertake regeneration when the radial nerve is injured, or to the newly-formed nerve fibers from the uninjured parts which grow into the anesthetic region and produce regeneration. Fessler[24] does not support this theory, but believes the fibers of the radial are important in the retention of the sensibility.

Pain. In complete division of the nerve no pain is experienced. If the nerve is injured or compressed by organized callus or scar tissue, the sensation of pain is most evident a few days after the injury.

Clinical Examination. In determining the extent of the injury it is necessary to obtain a careful history of the accident and symptoms, as well as to examine the injured parts and test all muscle groups and sensory areas.

If possible, it should be decided whether the nerve is completely divided or merely traumatized. The function may be lost below the seat of the injury, either because the nerve has been divided, traumatized, or compressed by callus. It is frequently difficult to judge the exact condition, particularly if the injured part is examined immediately after the accident, when the symptoms are severe. In such cases, the sensory examination is very frequently ineffective as numerous anastomoses exist in the hand, and the maximum puncture may be of no value. An electrical excitability test does not give deciding data, as it is rendered difficult through swelling, and excitability of the peripheral nerves may still be possible. The presence of motor signs may be of no value, as they may show remaining power or may indicate the beginning of repair.

Muscles. All the muscles supplied by the musculospiral nerve should be tested for movement, tone, reflexes and atrophy. The power of the extensors of the wrist should be tested with the fingers flexed on the palm, as any slight contraction in the extensors of the wrist may then be felt. The extension of the proximal phalanges should be noted. The extension of the thumb must be carefully distinguished from the movement of abduction, the latter being controlled by the median nerve. If the examiner discerns a slight trace of movement, spontaneous recovery may be expected.

Electrical Diagnosis. In making the electrical examination, the use of the Victor Multi-plex Sinusoidal apparatus with a diagnostic electrode and 6 by 8-inch disbursing indifferent electrode is recommended in the U. S. A. Manual of Neuro-Surgery. The indifferent electrode is moistened and placed over the abdomen or back. The diagnostic electrode is applied over the motor point of each muscle to be tested. Sufficient current is used to obtain a contraction but not enough to stimulate the adjoining muscles. The patient lies relaxed. The faradic current is first used if a normal reaction to electrical stimuli is obtained. The presence of faradic irritability after ten to fourteen days means that the nerve will recover spontaneously, since it shows at once that reaction of degeneration is not present. If faradic irritability is diminished, then galvanic current is used and the speed of muscle contraction and the amount of current required, are noted. A feeble, sluggish contraction is an indication that the nerve has degenerated. A brisk galvanic reaction, even though faradic excitability is absent, is an indication to adopt an expectant line of treatment.

Skin. Methods for the examination of the sensory conditions have been outlined in the U. S. A. Manual of Neuro-Surgery. The epicritic sense is tested by shaving the skin and turning a camel's-hair brush over it. The protopathic sense is tested with a sharp pin on the end of a 6-inch stick. Deep sensibility is determined by the pressure of a pencil. It is rarely that some definite area of sensibility is not found following lesions of the musculospiral nerve.

Hamilton[32] studied 55 cases at the Walter Reed Hospital to determine the areas of sensibility to pressure, pin-prick, and cotton or camel's-hair touch. He found that the patient fails to recognize subjectively and with any degree of accuracy the area of sensory loss, especially of the epicritic sense. Twenty-seven cases showed a definite area of sensory involvement in the forearm and hand. There was only 1 case in which the musculospiral nerve had been injured sufficiently high to produce loss of sensation corresponding to all three branches.

Vasomotor and trophic changes in the condition of the skin, nails, muscles, joints and bones should also be noted.

Types of Injuries. Injuries to the musculospiral nerve may be divided into two groups.

1. Immediate loss of function from traumatism.

2. Loss of function from pressure, callus, or scar tissue, usually associated with fractures, and occasionally following crushing injuries.

In primary division the onset of the paralysis is sudden. In secondary cases the paralysis develops insidiously and the functional loss increases as compression takes place. In case of injury coincident with or immediately following a fracture, the nerve may be bruised, stretched, compressed between the bone fragments or

impaled by a spicule of bone. The nerve may be completely divided or the fibers may be crushed without damage of the nerve sheath. Goldstein[29] found 12 cases of complete division out of 20 cases of paralysis due to injury at the time of fracture, and he believes that complete division usually occurs at the time of primary injury.

Complete division of the nerve results from fractures or from direct injuries such as occur in stabbing accidents. Such cases should be sutured as soon as possible. This type is illustrated by the following case.

Case I. In the course of a fight this patient, T. G., had been stabbed in the right arm. Two months later he began to notice that he could not close his hand or pick up things. When we first saw him, four months after the injury, he had right wrist-drop, no sensation in the posterior radial side of the hand, and no power in the supinator longus or extensor groups. Operative interference was advised.

Operation. After a careful preparation, a 5-inch incision was made on the outer side of the arm. Upon exposure of the nerve, the upper end revealed a bulb almost as large as the end of the little finger, and the lower end was entirely separated and involved in scar tissue. By means of a safety-razor blade, $\frac{3}{8}$ of an inch was removed from each end. The nerve sheath was sutured with interrupted linen, and the nerve surrounded by fat. The muscles were sutured together loosely. The skin was closed with silkworm gut and the arm strapped in 45° flexion. A hyperextension splint was applied to the forearm and hand. This position was maintained for three months.

Six months after operation, power began to return in the wrist. Baking, massage and gentle movements were advised. Fourteen months after the operation, Dr. Earle E. Hussey, of Fall River, examined the patient and sent the following report:

At the elbow-joint, all motions were free and unlimited. The muscular power to flex and extend the forearm was very good. The patient complained of an aching sensation in the upper third of the forearm, but there was neither tenderness nor loss of sensation.

At the wrist-joint, the patient could move the hand freely in all directions. He could dorsiflex the wrist and had good power in the flexor and extensor muscles.

The Fingers. He could make a good fist; his hand grip was about one-half power. The power of flexion and extension was good. The terminal joints of all four fingers were stiff; all the other joints were free.

Loss of function may occur from hemorrhage which has become organized into scar tissue, which in turn involves the nerve and constricts the trunk.

CASE II. B. M., hurt her arm in an automobile accident in November, 1921. She suffered a deep muscle injury about 4 inches above and anterior to the external condyle. The wound healed in three weeks, but the patient was unable to dorsiflex the wrist and fingers. She was seen from the first time on December 27, 1921. There was a deep adherent scar, and considerable numbness over the lower external humeral region. The biceps and triceps were present and the patient could make a fist. There was no power in extension of the wrist or fingers, in spite of their having been held in hyperextension for six weeks. The patient had suffered also a fracture of the left clavicle and numerous other injuries. She was advised to enter the hospital for an exploratory operation.

FIG. 1.—Case II. B. M. Showing return of voluntary power in extension of wrist and fingers, one year and three months after freeing nerve from scar tissue.

Operation. January, 1922: After a careful preparation, the musculospiral nerve was exposed by a curved incision. The nerve was found to pass through scar tissue that had developed at the site of the wound. This scar tissue was excised and the nerve thoroughly freed. It was found intact and there was no bulbous end. The nerve was placed in a new muscle bed. The arm was kept at a right angle without motion for eight to ten weeks. The temperature remained normal. The wound was dressed for the first time on the fifth day. Seven weeks after the operation the patient was measured for a hyperextension splint for the fingers.

April 18, 1922. There was slight power in the extensors of the wrist.

May 16, 1922. The patient had regained power in the extensors on the radial side, but not on the ulnar. There were 20° of motion in flexion and limited extension in the elbow-joint, and it was

expected that these motions would increase. The patient was advised to continue massage.

August 4, 1922. The arm was greatly improved. The extensor return, except the extensor pollicis, was very good. Patient was advised to continue wearing the splint and to exercise the fingers daily for fifteen minutes.

September 6, 1922. The restoration of muscle control in the wrist was complete except for the extensor of the first metacarpal. The brace was discarded.

March 20, 1923. One year and two months after the operation, there was perfect flexion and extension at the elbow, good supination and pronation, and complete return of the musculospiral nerve distribution. The patient could separate the fingers. The thumb and index finger were slightly numb and the hand showed a little atrophy of the thenar eminence. The patient could not make a strong grip. (Fig. 1.)

Loss of function from pressure occurs following fractures of the humerus in which the nerve root is usually enveloped by callus or scar tissue that forms about the site of the fracture or injury.

Case III. This was a case (J. L.) of injury to the musculospiral nerve following a comminuted fracture at the middle and the lower end of the left humerus with non-union. The nerve was compressed and caught in callus and scar tissue.

October 4, 1921. One year and six months after the injury, the patient was seen for the first time, and advised to have an immediate operation.

Operation. A lateral incision was made, exposing the field of non-union. The upper end of the musculospiral nerve where it enters the groove was located and dissected free from the groove for a short distance. As it then entered dense scar tissue it was necessary to locate the lower end of the nerve which was dissected upward from below. This lower end also entered the scar tissue, and it was only by careful and tedious dissection that the nerve was freely removed from this area without damage. (Fig. 2.)

The nerve was carefully examined and although there were a few areas of local swelling, no definite division had taken place, and there were no bulbous masses within the sheath.

The area of non-union was then explored and a graft removed from the tibia, was inserted and held in the humerus by kangaroo suture. A new bed was made for the musculospiral nerve and the wound closed.

A plaster was applied from the fingers over the shoulder and about the chest. The wrist was held in hyperextension.

January 24, 1922. As the radiogram showed no union, the cast was not removed.

March 27, 1922. Callus formation was beginning and the graft

was firm. The plaster was taken off (now six months), but protection was continued.

January 22, 1924. Union was solid. The shoulder was normal. Flexion and extension were perfect. Supination was limited a few degrees. The patient could make a fist, but the fourth and fifth fingers were contracted at the second phalangeal joints. There was complete regeneration of the extensor control. The patient was back at work and had a very functional hand.

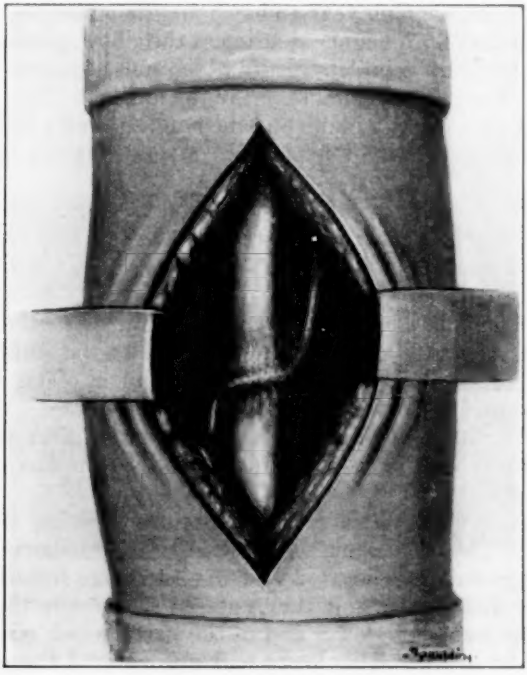

FIG. 2.—Case III. J. L. Showing area of non-union with musculospiral nerve caught in cicatricial tissue.

Prognosis. In general, operative results have been satisfactory. Kramer[43] reported 35 cases with only 3 poor results. Blenke[5] reported 58 cases, 41 of which made complete recovery, 6 partial recovery, 8 improved, and 3 showed little improvement. In some cases failures have been due to neglect of aseptic requirements or to lack of postoperative care.

Surgeons disagree as to whether recovery is better after nerve suturing for primary injuries, or following operation for paralysis due to the involvement of the nerve in scar tissue or callus formation. Sherren[73] and others have found that recovery may be perfect after a primary suture, but that it is not so good following secondary

operations, as sensory recovery is rarely perfect. Borchard,[6] on the other hand, claims that operation for secondary injuries results more favorably because in primary suture any neglect of aseptic requirements is followed by failure of nerve suture.

Although the prognosis is better if the interval between the injury and operation is short, still there is a chance of complete recovery after a long period of paralysis. Cases operated after sixteen months or even after three and a half years following fracture have resulted in complete restoration of function.

The establishment of continuity by end-to-end suture offers a greater chance of success than any other operative procedures such as grafting, implantation, or transplantation of nerve.

Indications for Exploration. Any open wound over the musculospiral nerve accompanied by wrist-drop, should be enlarged and the nerve examined. If a division of the nerve is present, a suture should be done at once.

If the nerve is injured from a blow in which it seems probable that complete division has taken place, suturing should be done early. Sometimes, however, the bruised condition of the soft parts is such that it is necessary to postpone a needed operation until the hemorrhage is reabsorbed, and a favorable opportunity offered for the healing of the wound. If the exact condition of the nerve cannot be determined, it is well to wait to see if power returns spontaneously. During this period, however, the fingers and wrist should be held in hyperextension, which position always favors the return of muscle power.

In the presence of fractures accompanied by radial paralysis in which it is impossible to determine whether paralysis is due to contusion or sectioning, it is best to first obtain reduction of the fracture and apply plaster. The muscles should then be watched for signs of atrophy and the fingers and the thumb should be exercised daily. If, after three or four months, paralysis still persists, exploratory operation should be performed.

Operative Technic. The method of treating the nerve must vary according to the pathological findings. If the nerve is found intact, often only a simple operation, such as removing the bone over which the nerve is stretched, or removing scar tissue or excessive callus, may be necessary to give relief.

Frequently, however, the nerve may be completely divided, constricted, torn, or bulbous at one end. In such cases, the usual procedure is to excise the affected portion, freshen the nerve ends, and establish continuity by suture. Nerve sutures have given very gratifying results and are recommended by many operators, including McCurdy,[48] Keen,[42] Cheyne,[13] Eve,[22] Ashhurst,[1] Auvray,[2] and many others.

Author's Technic. The approach to the part of the nerve involved is most successful if the upper and lower parts outside

the field of injury are located and a dissection made up and down to the seat of damage. This approach is not only much safer but quicker than other method. When the ends of the nerve are found bulbous, or a distinct swelling or constriction is felt in the nerve trunk, it is best to cut out this section by means of a safety-razor blade. The ends are then approximated and the entire sheath about the nerve sutured with linen. In cases of division of the nerve in which retraction has taken place it is often necessary to place the arm in flexion to gain approximation. It is rarely necessary to shorten the humerus.

After the ends have been sutured, the nerve should be placed in a new non-scar tissue bed, usually between layers of fat or muscle. There is some discussion as to whether fat is the best substance to prevent the formation of adhesions. Henle,[35] Morris[50] Williams,[81] and many others approve its use. Other operators believe that the fat atrophies, and they recommend the method used by Fessler[24] and Grisson,[31] of wrapping the nerve in a muscle flap of the triceps or of the brachialis.

The elbow should be held in flexion for at least five to six weeks, and then gentle passive motions may be started. The wrist and fingers must be held in hyperextension to avoid flexion contraction, to favor muscle regeneration, and to prevent the stretching of the extensors which, in itself is an important factor in hindering the return of muscle power.

As soon as motion begins to return, graduated massage and muscle training are of great advantage. The time when improvement begins varies from a week to several months. Motion usually begins to return in three or four months and it is usually a year before restoration is complete.

It may happen that after excision of the affected portion of the nerve, too large a gap exists to allow the approximation of the nerve ends. Such a condition is not frequently found in civil life, but war injuries often destroy a large part of the nerve. Several means have been used to bridge the space.

Piper,[60] Morton,[51] and Sherren[73] advised the manual stretching of the nerve and suture after the ends were in apposition.

Plastic neurotomy was used with success by Harrison[33] who turned into the space a flap from the upper end of the nerve which was bulbous. Dawbarn and Byrne[15] bridged a 3-inch gap by splitting the nerve at a low point of its distal portion and swinging the long shaft thus made into the space. Sherren[73] believed a flap should be used as rarely as possible, because such an operation necessarily is technically complicated.

Implantation of nerve, the method of attaching the stump of the distal end of the severed nerve to a healthy nerve, was first proposed by Lobker.[46] Roques de Fursac[70] implanted the musculospiral nerve in the median. Barkley[3] anastomosed the proximal

and distal ends with the median. Auvray[2] formed an anastomosis of the lower end of the radial with the internal brachialis cutaneous nerve. These procedures are of little value if the fibers of the healthy nerve are not separated and such an operation is difficult.

A few successful results from nerve grafting have been reported. Auvray[2] transplanted successfully a portion of the internal brachialis nerve 10 to 12 cm. long between the two freshened extremities of the musculospiral nerve. Sherren[73] suggested using for grafts the internal saphenous nerve obtained from the patient or from a recently amputated limb. Neuhof,[57] in a recent article on the transplantation of nerves in general, stated that as yet it was impossible to estimate the value of nerve transplantation. Only a few successful results have been obtained and the cases in literature have been recorded too early to judge the final result.

Still other means of bridging the gap have been suggested. A tubular suture has been proposed by some surgeons. Sherren[73] preferred a tube composed of one of the patient's superficial veins. Foreign materials have also been used. Keen[42] applied catgut threads, and Morris[50] bridged a gap of 3 cm. with silk thread. Magnesium was tried, but it was found to harden. Reisinger[68] proposed sinking the nerve in the triceps muscle and fixing it there.

Resection of the humerus as a means of allowing the approximation of the nerve ends is justifiable only in cases of ununited fractures complicated by division of the nerve. Ollier[59] has reported early cases of resection. Keen[42] reported using this method in 1 case and Riethus[69] in 3 cases.

If the damage to the musculospiral nerve is irreparable by the use of any of the methods mentioned, or if a case has not been relieved by end-to-end suture, then tendon transplantation is a commendable procedure. Its object is the improvement and restoration of muscle balance in the hand.

As the extensors of the wrist and fingers have lost their power, the problem is to transpose some of the muscles on the flexor aspect of the forearm without interfering with the power of flexion. The flexor carpi radialis, the flexor carpi ulnaris, and the pronator radii may be relied upon for this procedure.

Author's Technic. The attachment of the flexor carpi radialis is severed through a 1-inch incision made directly over it on the anterior surface of the wrist. A second incision is made half way up the forearm along the course of the flexor carpi radialis tendon, and the tendon pulled up. A long L-shaped incision is made across the back of the wrist and up the side of the ulna. The flap is dissected upward, the tendon of the flexor carpi radialis is thrust obliquely over the edge of the radius and made to appear over the back of the lower end of the radius. (Fig. 3). The ulnar tendon is severed at its attachment, carefully dissected upward as far as the

incision permits, and the whole muscle turned over, so that the tendon lies along the back of the lower end of the ulna.

During the completion of the operation the wrist and fingers are held in hyperextension. All the extensors are split to receive

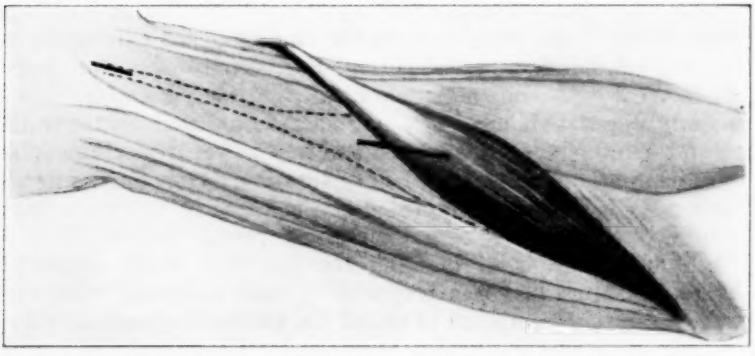

FIG. 3.—Showing incisions over attachment of flexor radialis and along the course of the tendon. The tendon is thrust obliquely over the edge of the radius.

these tendons, which are crossed through them (Fig. 4.). The thumb extensors are also included in those cases in which special provision has not been made for the extension of the thumb by the use of the pronator radii teres or the palmaris longus.

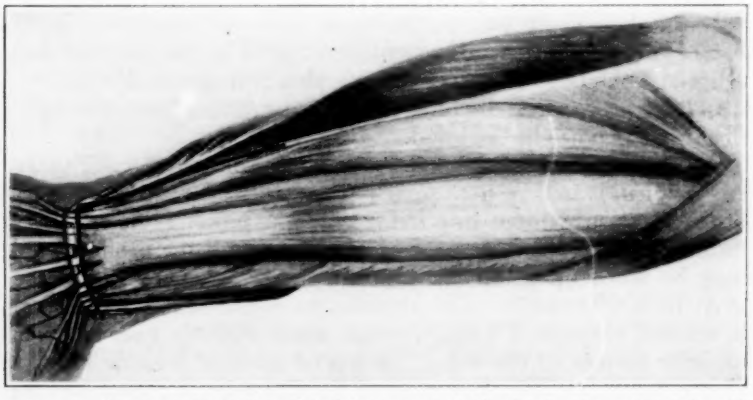

FIG. 4.—Showing the L-shaped incision across the back of wrist and up the side of ulna. The ulnar tendon has been severed at its attachment and the whole muscle turned over. The radial and ulnar tendons are seen running through the extensors which are slit to receive them.

The wound is closed. A splint is applied with the wrist and fingers held in hyperextension. This is worn for six to eight weeks during which time massage and passive motion are carried out.

CASE IV. F. A., was ill in 1916 with acute arthritis of the shoulder. After an operation in which some dead bone was removed, wrist-drop and loss of elbow motion were noticed.

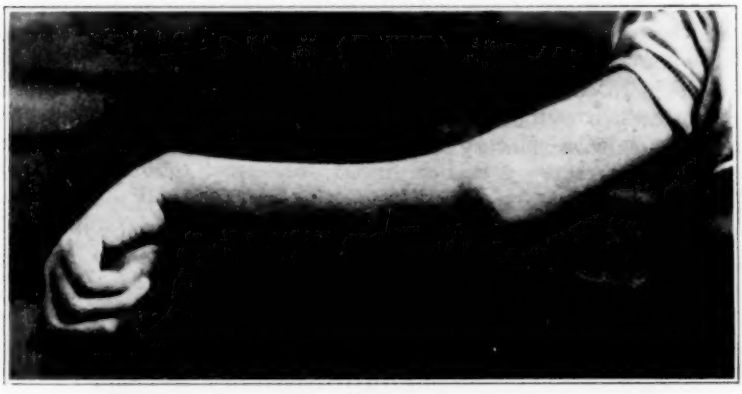

FIG. 5.—Case IV. F. A. Showing wrist-drop and hand deformity before tendon transplantation.

January, 1917. The patient was seen for the first time. Radiograms showed a diffuse osteomyelitic process involving the whole humerus. The shaft was opened *in toto* and four days later the patient was able to extend the fingers, showing some power in the radial nerve.

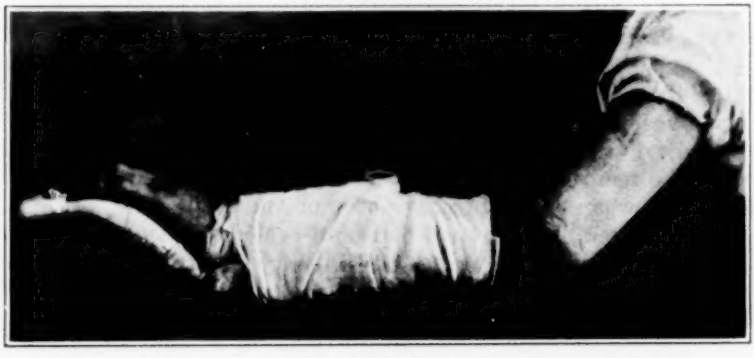

FIG. 6.—Case IV. F. A. Hand in splint after tendon transplantation.

September, 1917. The patient discarded the leather brace he had been wearing and a small hyperextension hand splint was applied. A radiogram later showed complete regeneration of the humerus. Daily olive oil massage and constant use of the hand were advised.

November 5, 1919. The power of extension of the wrist had not been regained (Fig. 5). A tendon transplantation was performed according to the above technic.

November 29, 1919. Massage and muscle training were started.

December 8, 1919. The patient was able to hyperextend the wrist.

September 8, 1920. He had voluntary extension of the wrist to within 15° of normal, and voluntary extension of the fingers to within 20° to 40° of normal. The extension of the thumb was deficient, but satisfactory (Fig. 6).

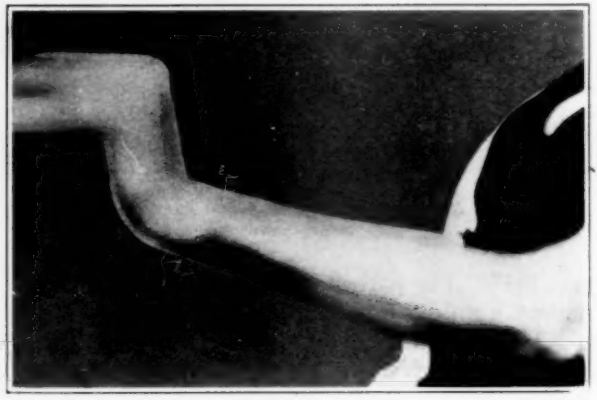

FIG. 7.—Case IV. F. A. Voluntary extension four years after tendon transplantation.

CASE V. M., admitted to the Alder Hey Hospital September 26, 1917, had suffered a compound fracture of the right humerus and severance of the musculospiral on May 9, 1915.

History. He had been treated in France, having had 7 operations for removal of shrapnel and cleaning of wound. The last operation was supposed to have been on the nerve.

Examination. The wound had been healed eight months. The present complaint was wrist-drop. Two long scars were attached to the bone in the upper arm. The humerus was shortened and irregularly thickened in middle and lower thirds. There was no power in the extensors of forearm. There was slight sensory loss over first phalanx of thumb. From the depth of the density of the scars, a wide gap of nerve seemed probable.

Electrical Reactions. The median and ulnar sensations were not affected. The radial sensation, E. and P. was impaired on the whole dorsal surface of the thumb, and slightly over the knuckle of the index finger. The forearm sensation was not affected over the musculospiral area. The extensors of the thumb, F.a., G.

faint, K. C. C.) A. C. C. Ext. communis, F.a., G. fair K. C. C.) A. C. C. The ulnar and median muscles were normal.

Diagnosis. The musculospiral nerve was involved in callus.

Treatment. On October 9, 1917 an operation was performed by Dr. A. R. MacAusland. Through a 5-inch incision, the musculospiral nerve was exposed just above the elbow, and followed up about an inch into very dense scar, where its course could not be traced farther. Without disturbing this region to any extent, the nerve was exposed on the axillary side as it entered the musculospiral groove, where it was found to be free for a short distance. It then entered dense scar tissue, but was carefully traced for about 1 inch more to the region of the very deep posterior scar. The dissection was completed through the incision on the outer side of the arm. The nerve ran into scar with only slight tendency to bulb. Exploration of scar farther revealed no nerve elements. The gap of about 3 inches was filled in with a section of the cutaneous nerve from the inner side of the musculospiral nerve in the axilla. It was not possible to bring the nerve ends together with graft, even by the expedient of crossing it in front of the humerus.

October 12, 1917. No pain, no temperature.

October 23, 1917. Clean; healed. Tendon transplantation seemed advisable.

November 13, 1917. Operation: Tendon transplantation. Flexor V. rad. into extensors of thumb, extensors longior and brevior and other extensors.

November 14, 1917. The patient had considerable pain. The circulation was good.

November 19, 1917. The patient was much more comfortable. He was advised to wear a long cock-up splint, with strap and thumb piece.

November 23, 1917. The thumb was to be extended. The wound showed slight sepsis.

November 26, 1917. The wound was clean. A short cock-up splint was to be applied.

Transplantation of the tendons for musculospiral nerve paralysis has been a most successful operation, as the tendons used are constant and strong. The early attempts to convert tendons into ligaments were made by Tilanus,[75] Codivilla,[14] Reiner,[67] and Gallie.[26] Jones,[39] Francke,[25] Müller-Aachen,[54] Vulpius,[80] Drobnik,[19] and Murphy[55] advocated this procedure in cases of extensive destruction of the nerve.

Jones[39] has outlined a tendon transplantation operation in which he converts the three extensors into ligaments so that the carpus can be fixed in the best functional attitude of dorsiflexion and still permit movement at the wrist-joint, but not in the direction of the deformity.

His operative technic consists of making a 3½-inch incision from just above the back of the wrist-joint extending up the middle of the forearm. By retracting the extensor ossis metacarpi pollicis and the extensor brevis pollicis, the two radial extensors may be followed along the forearm and divided high up and the ends pulled down. A tunnel is then drilled across the radius from the outer side, a little over an inch above the line of the wrist-joint. After the tendons have been scarified the extensor carpi radialis longior is pulled through the tunnel from the outer side and the brevior from the inner side. Their ends overlap and are sewed with a continuous catgut suture. In the same way the extensor carpi ulnaris is followed up to the forearm, divided, and the ends drawn through a tunnel in the ulna. Any tendency toward radial deviation of the hand by the pull of the radial extensor is thus corrected. The hand and forearm are encased in plaster. It is important to support the hand in the dorsiflexed position from the time the first catgut suture is inserted until the last plaster bandage is applied. In two or three months the patient may use his hand.

In a case of complete paralysis of the nerve Müller[54] tried tendon transplantation by cutting the tendon of the flexor carpi ulnaris and uniting it with the extensor tendons of the fingers. Seven months later the tendon of the flexor carpi radialis longus was cut and sutured to the tendon of the abductor of the thumb and the extensor carpi radialis longus. The patient was then capable of lifting the hand to a horizontal position and of abducting the thumb.

Murphy[55] released the flexor carpi radialis dorsally for 4 inches by tunneling through a button-hole incision. It was passed subcutaneously downward to the upper margin of the posterior annular ligament. The extensor tendons of the thumb and of each finger (two for the index and two for the little finger) were transfixed. The tendon of the thumb and of the index finger were attached obliquely from above downward and inward so that extension would not bring the inner three fingers into play ahead of the thumb and index finger.

Vulpius[80] reported 28 cases of tendon transplantation and Drobnik[19] reported 16 cases.

Sir Robert Jones[40] makes use of the pronator radii teres to produce extension of the wrist, by inserting it into the two radial extensors, and the flexor carpi radialis and the flexor carpi ulnaris to produce extension of the fingers and thumb by insertion into these tendons. During the whole procedure of tendon suture he keeps the wrist and fingers in complete dorsiflexion and the thumb in full abduction in order to procure the best action from the transplanted tendons. After operation the limb is placed in a splint which keeps the wrist in full dorsiflexion and the metacarpophalangeal and the interphalangeal joints flexed at an angle of about 10°.

Jones has used this technic in 20 cases. All the patients were

able to dorsiflex the wrist with the fingers closed and then to extend the fingers while the wrist remained in dorsiflexion.

Pathology. In operating for musculospiral nerve paralysis, the nerve is often found intact, but stretching over bony fragments or involvement in scar tissue or callus prevents it from having normal power.

If the nerve is crushed or torn the changes differ from those which occur as the result of severing by a sharp knife. In the latter case there is no contact between the two ends of the nerve and the changes differ in the proximal and distal parts. The proximal end becomes markedly bulbous. The distal end becomes shrunken, tapering, or slightly bulbous.

If the nerve is crushed it becomes inflamed and the inflammatory condition may lead to complete destruction. The nerve sheath may not be damaged, but the nerve fibers being inflamed, a constriction or a bulbous formation may develop within the sheath.

Reparative Processes. The regenerative process depends upon the trauma, the pathology and nourishment of the nerve.

Henriksen[36] made experimental investigations to determine the exact regenerative processes in a nerve that was completely divided and in one damaged in a crushing injury. He found that after complete division regeneration begins immediately, developing most rapidly in the central stump where fully organized myelin fibers may exist as early as ten days after injury. The first histological sign of regeneration is activity of the neurilemma nuclei which begin to proliferate. The protoplasm at the poles of the nuclei increases and grows into thin threads through the old Schwann sheaths and out into the severed nerve ends forming a bridge between the latter. Henriksen found that in the course of a few days these threads may bridge a gap of more than 0.5 cm., and that the old Schwann sheaths are pierced by long protoplasmic threads before the old threads have completely lost their structure. Fully characteristic nerve segments may be found in the central stump ten days after severance.

When a nerve is severed, its muscle loses weight and degenerative changes occur. At the same time the sarcolemma nuclei become active and new cellular matter forms in the muscle. When innervation begins, these cells form the basis for the formation of young muscular fibers. It is difficult to tell just when the muscle regains tone, but it may be late, five to six weeks after a primary suture.

Henriksen, in experimenting on rabbits, could find no essential difference in the process of regeneration when the nerve was sutured or when it healed unaided. In fact, the nerve fibers were at first found deflected as a result of the pull of the thread, although later they straightened out. Nerve suture, however, is necessary when obstacles prevent spontaneous healing.

One would naturally assume that a crushed nerve would regenerate

more easily and quickly than a severed nerve, but clinical examinations show that physiological restitution is often not so complete and is often slower in a case of a crushed nerve. The nourishment may be established more rapidly, but disturbances may appear in the process of regeneration, or the myelin differentiation may be disturbed, thus hindering the healing. After a complete severance of the nerve, the mass growing out from the ends to form the bridge between the ends thickens, and the nerve recovers its smooth appearance. If the nerve is crushed the thickness is uneven and it infiltrates the surrounding tissues. The peripheric part of the nerve is swollen and edematous.

Literature. After von Busch[10] and Ollier[59] in 1865 reported good success in operating in cases of paralysis following fractures of the humerus, many similar cases were recorded in literature. In 1886, von Bruns[9] reported 189 cases of nerve injuries. Seventy-three of the 138 cases of the upper extremities were musculospiral nerve paralysis following fractures of the humerus.

In 1889 Bowlby[7] issued statistics of the operated cases that had been published. All the cases, 2 by Trélat,[77] 2 by Bidder, 1 each by Erickson, Ollier, Whitson, Delans, Israel,[38] Tillaux,[76] and Hueke had resulted from fractures of the humerus and were due to stretching, contusion or pressure. The results in 7 of these cases were satisfactory.

Goldstein[29] in 1892, Wölfler[83] in 1895, Neugebauer,[56] Zoege-Manteuffel,[84] and Drewitz[18] in 1895, reported several cases in which the nerve was found compressed in scar masses or bony callus. Successful results were obtained by operative interference.

In 1899 Riethus[69] described fully 7 of his cases. In 5 cases the nerve was compressed by bony callus or fibrous tissue. Complete cures were effected by operative interference in 2 of the cases and essential improvement was obtained in 2 cases. The result in the fifth case was not reported. Excellent results were obtained in 2 other cases in 1 of which the nerve was stabbed on the edge of a fragment of bone, and in the other in which the nerve was stretched over a sharp bony edge.

The same year Willmers[82] reported a successful result.

In 1900, Keen[42] reported a series of 7 cases, in 6 of which operations were performed for paralysis of the musculospiral nerve following fracture of the humerus. Complete restoration of function was secured in 2 cases by suture of the nerve. A useful arm was obtained in 1 case in which the humerus was resected to approximate the ends of the nerve over a gap of 5 cm. As the other patients did not carry out the postoperative requirements, very little improvement took place in 2 cases and no improvement in 1 case.

In 1 case of complete division of the nerve by a knife blade, Keen sutured the nerve ends with silk thread. Fourteen months later the patient had a good, useful hand.

Launois and Lejars[44] reported a successful case in paralysis following a fracture.

Braüninger,[8] Kramer,[43] and Reisinger[68] also reported good results in freeing the nerve from compression.

In 1905, Piper[60] published his monograph on the subject of musculospiral nerve paralysis following fractures of the humerus. After reviewing the literature from early times and describing the various types of operative technic, he cited 4 cases from the Kieler Clinic. One case was not operated. The second in which the nerve was pleated and a layer of the triceps laid between it and the bone, resulted in a weak hand. In the third case the nerve was found intact, but twisted above the seat of fracture: paralysis was overcome by freeing the nerve. In the fourth case the nerve was intact but involved in callus. The definite outcome of the operation was not recorded, but the latest record was the beginning of a degenerative reaction.

Scudder and Paul[71] reported 11 cases of suture in the Massachusetts General Hospital. Eight cases were relieved by operation. The other 3 cases were failures.

Of 12 cases reported by Borchard[6] in 1907, 2 were unsuited for operative handling; in 2 cases the nerve was sutured; in 3 cases it was simply loosened from adhesions; in 3 cases bony masses and scar tissue were removed; in 1 case it was necessary to excise the radial head, and in the twelfth case nerve grafting was employed to bridge a large defect. Except in the last 2 cases on which it was too early to report, the condition was cured by operation.

In 1909, Harrison[33] reported 2 cases, 1 in which the nerve was compressed by callus and 1 in which the nerve crossed in front of the humerus. Operation on the first case in which a flap of the nerve was turned in to bridge a wide gap, resulted in a good serviceable hand. In the second case it was necessary to divide the humerus in order to place the nerve in position. In three and a half months the patient could extend his hand to an angle of 150° with the forearm, and further improvement was expected.

Els[21] reported 2 cases of secondary suture. Perfect function resulted in the first case from operation for partial tearing of the nerve over a bony fragment. The result in the second case of paralysis due to the involvement of the nerve in scar tissue, was good, but the hand was somewhat weak.

Charbonnel[12] reported a case of double fracture and splintering of the humerus followed by nerve paralysis. The nerve was freed from between the long supinatus and the anterior brachialis, and in six and a half months the patient had normal movements.

Barkley[3] reported a case in which the humerus was broken in two places, and there was a loss of 4 inches of substance of the nerve. The ends were anastomosed with the median nerve, and complete use of the hand resulted.

In 1911, Morestin[49] reported 3 cases on which he had operated. In 1 following fracture of the humerus, the nerve was freed from between the fragments and sutured, and in one month there were good prospects for success. In the second and third cases of paralysis, likewise following fractures, the nerves were found embedded in callus. Fifteen days after operation in the second case, the patient could extend the hand and fingers almost to normal. Operation on the third case also resulted in the return of all normal movements.

Schwartz[72] operated for a case of paralysis following fracture of the humerus. He freed the nerve from callus and interposed a layer of muscular and fibrous tissue between it and the bone. In ten months recovery was complete.

Gaudier and Deladrière[28] reported a case of paralysis following fracture of the humerus. Five months after the nerve was freed from adhesions the patient had recovered all movements.

In 1912, Nikoloff[58] cited a case in which the paralysis appeared three weeks after the healing of a fracture of the humerus. To bridge the gap, a tube of fibrous cord was made and the non-paralyzed end of the nerve sutured to the paralyzed end. A muscle layer was inserted to separate the nerve from the bone. A complete return of movement was obtained.

Judet[41] cited a case of secondary paralysis following fracture of the humerus in which the nerve was found compressed by a spicule of bone. Operation resulted in a complete cure.

Ferraton[23] sutured a nerve that had been destroyed in a comminuted fracture of the humerus caused by a bullet. All movements of the hand returned.

Murphy[55] reported establishing end-to-end union of the nerve by applying a flap. In another case he united the ends of the nerve at the central septum to the triceps muscle. He did not report his results.

Gallois and Tartanson[27] reported 2 successful cases in which paralysis had followed fractures. After isolation of the nerve from the callus, a layer of muscle was inserted between it and the bone to prevent further complications.

In 1914, Mosti[52] cited a case of secondary suture that resulted in complete success. Quénu[64] also reported a successful case of secondary suture. Hohmann[37] operated on 1 case of paralysis following fracture of the humerus.

In 1916, Dawbarn and Byrne[16] did a splitting neuroplastic operation in a case of destruction of the nerve from a fracture of the humerus. An irregular form of regeneration resulted.

Successful results from suturing of the nerves were reported by Souques,[74] Loewenstein[47] and Ranschborg.[65] Moszkowski[53] presented a case in which a pedicled flap of the triceps muscle was used to bridge the defect in the nerve. At the time of his report

it was too early for complete restoration but signs of regeneration were apparent. Two successful nerve suture operations for complete division of the nerve were presented by McCurdy[48] in 1917.

Beck[4] operated for a paralysis resulting from a fracture that had occurred seven months before. In operation a tubule of fascia lata and fat was transplanted into the extensor tendons. Twelve weeks after the operation, considerable power had returned to the muscles.

Morris[50] reported a successful case of secondary suture for paralysis following non-union of a fracture of the humerus. In discussion of his report, Green and Hitzrob reported similar cases in which they had been successful.

Hartwell[34] reported a case of a successful suture forty-six days after section of the nerve by a stab wound.

Due to the frequency of injury to the musculospiral nerve in war wounds, there were many operations performed between the years 1917 and 1921. Gosset,[30] in 1923, summed up very well the results of these operations.

In 1917, Gosset,[30] himself, reported 144 cases. In 44 cases of freeing of the nerve, there were 26 successful results, 10 cases of improvement, and 8 failures. In 27 cases of suture for complete sectioning, there were 16 good results, 1 case of improvement, and 10 failures. In 2 cases of suture for incomplete sectioning, there was 1 cure and 1 failure.

In 1918, Gosset and his pupil Charrier studied 76 cases. In 18 cases in which the nerve was freed from compression, 95 per cent recoveries were obtained. The condition of the other patients was improved. Thirteen cases of complete sectioning in which the nerve was sutured, resulted in 4 recoveries and 3 failures due to bad technic. The condition of the other 6 patients was slightly improved. In 21 cases of incomplete sectioning, there was a fibrous formation between the nerve ends which some operators believed might be used as a means of conductivity. In the 5 cases in which this tissue was utilized there were 4 failures. In the other cases the fibrous formations were excised and an end-to-end suture was done. There were 9 good results, 4 cases of improvement, and 3 failures. These results show clearly that the fibrous formations do not act as conductors of nerve influence.

Dumas[20] reported the results of 115 cases that were operated upon. In 18 cases of freeing the nerves from compression, 83 per cent good results, and 11 per cent fair results were obtained; in 41 cases of incomplete severance 70 per cent successful results and 11 per cent fair results; in 46 cases of sectioning with some fibrous continuity remaining, 43 per cent successful results, 10 per cent fair results and 46 per cent failures; in 10 cases of complete severance treated by suturing, 1 fair result. The other cases were failures.

In 1918, Delagénière and Tinel[17] reported 181 sutures with 88 per cent positive results. Villard[79] reported 8 suture operations with 4 good results.

Reder[66] reported a case of complete paralysis caused by a shot wound. At operation a strip of muscle taken from the head of the triceps was wound around the point of injury. In forty weeks all movements, except the ability to pick up a pin, were possible.

Auvray[2] in 1919, collected the results of 31 cases of wounds of the nerve operated in 1915. Of 15 cases of simple freeing of the nerve from compression, 7 patients obtained complete restoration of function; 4 an improved condition, and there was 1 failure; of 11 cases of end-to-end suture, 8 patients obtained complete restoration and there were 3 failures; 1 case of excision of a cicatricial nodule from the middle of the nerve was successful; and 1 case of nerve graft 10 to 12 cm. long from the internal brachialis cutaneous nerve resulted successfully. Three cases of anastomosis and redoubling of the upper end of the nerve were failures. On the average Auvray found amelioration had begun at the end of several months, usually four to eight.

In discussion of Auvray's report Wiart cited statistics less satisfying. Of 25 sutures, there were only 5 complete cures, and 5 cases of improvement; of 61 cases of freeing the nerve there were 20 complete cures, and 20 ameliorations.

In 11 cases of suture, Cestan[11] obtained 5 complete cures. The condition of 4 other patients was improved by operation. Two cases were failures.

Putzu[62] obtained 85 per cent cures in operations of freeing the nerve and 47 per cent cures in suture operations. Dane[15] secured 50 per cent good results. Platt[61] collected 35 cases of nerve suturing in which 26 very good results were obtained.

From the results of the above cases it is seen that operations of freeing the nerve give 95 per cent good results and suture operations give 45 to 55 per cent.

Henriksen,[36] in 1923, reported 5 successful cases in 2 of which the nerve was sutured, in 1 4 cm. of the humerus was resected to bridge a gap of 6 cm., and in 2 cases the nerve was freed from callus.

Conclusions. 1. The nerve may be injured in three ways: The nerve trunk may be crushed without damage to the sheath; the nerve may be completely divided; power may be lost through the involvement of the nerve in scar tissue or callus.

2. Early recognition and treatment of nerve injuries in connection with fractures and severe traumatisms is very important. We may expect a perfect result in cases of immediate suture of the nerve. While intervention in cases of old standing has given good results, it is the general opinion that the chances of success are lessened after the elapse of a long period of paralysis.

3. Simple freeing of the nerve is very often the only procedure necessary to relieve the condition. In cases of complete division of the nerve or in cases in which there is need to excise a portion of it because of a fibrous formation, nerve suture has been found the most satisfactory procedure for the approximation of the nerve ends. If the nerve suture does not relieve the condition, or if the case is not reparable by the various methods of manual stretching, neurotomy or nerve grafting, then tendon transplantation gives satisfactory results.

4. After severance of a nerve, healing begins spontaneously. In cases of nerve suture function develops in the same manner as in spontaneous healing. After secondary suture sensibility returns early. Muscle control usually appears in the course of two to four months and is complete in from six to nine months, depending upon the location of the nerve injury.

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A RAPID METHOD FOR THE DETERMINATION OF GASTRIC ACIDITY BY MEANS OF TEST PAPERS.

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The determination of "free" gastric acidity by titration with 0.1 N sodium hydroxid and dimethylaminoazobenzol (Töpfer's reagent) is a method which has found practically universal acceptance in the clinical laboratories in this country, and which has retained its popularity in spite of adverse criticism from several sources.[1]

In view of the fact that gastric digestion is dependent on the hydrogen-ion concentration of the stomach contents the idea of substituting a colorimetric hydrogen-ion determination for the titration method has been suggested by several investigators,[1] but most of these procedures have been rather too cumbersome to become popular in clinical work, on account of the large number of indicators and standard buffer solution required; the simplest and most practical being that suggested by Shohl and King in which one indicator, thymolsulphonephthalein, is employed together with a set of standards sealed in glass tubes, which if left in a dark place retain their original color for a relatively long time.* The method of Shohl and King, simple as it is, is sometimes difficult to carry out in the crowded clinic on account of the fact that as a preliminary it is necessary to centrifuge or filter the contents, and also because we believe that in order to get reliable results it is essential that a liberal supply of distilled water be on hand with which to rinse the glassware to be used in this test.

For more than a year we have been making use of test papers for the approximate determination of the pH of gastric contents. The use of test papers for this purpose is not new. McClendon,[2] in 1915, described a series of nine different test papers to be used in gastric contents and four for duodenal contents, and states that in his opinion the test paper is but little less sensitive for the determination of hydrogen-ion concentration than are solutions of the same dyes. Further experiments on the use of test papers for pH determinations in biological fluids have been described by Hass[3] and also by Felton.[4]

We have endeavored to prepare a single test paper which could be used with gastric contents of all degrees of acidity, but so far our search has been unsuccessful, and we have been compelled to

* A set of these standards which has been in more or less constant use for two years has recently been checked and found to be unchanged.

make use of papers prepared from two different dyes. Thymol blue for the range from pH 3.0 to pH 2.0 and dimethylaminoazobenzol (Töpfer's reagent) for the range from pH 2.0 to pH 1.0.

The papers are as follows: A solution of the dye in 95 per cent alcohol (0.5 per cent for dimethylaminoazobenzol, and 0.1 per cent for thymol blue) is poured over a sheet of filter paper six inches in diameter, the excess dye allowed to drain off, and the paper dried quickly by holding it in front of a rapidly revolving electric fan. The papers are then cut in strips of approximately 1 by $\frac{1}{4}$ inch in size, and stored in some receptacle in which they are protected from light and from the fumes of the laboratory. Only the highest grade of smooth "quantitative" filter paper should be used. We have obtained good results with the Arthur D. Little quantitative filter paper and with Whatman's No. 44, but probably any other grade of ash free paper would do as well. The gastric contents is removed in the usual way after an ordinary test meal, and a small portion of the material collected is poured over one end of a test paper. From the table of colors tabulated below it is then possible to tell at a glance whether we are dealing with hyper, normal, hypo, or anacidity. If a series of buffers of known pH are available a small quantity of one of these solutions of a reaction similar or nearly similar to what is believed to be the pH of the gastric contents (as determined by the color produced by it on the test paper) may be poured on another piece of the paper and the color so obtained compared with that produced by the unknown, but such a procedure while it is useful as a check on the readings, is not absolutely essential to one familiar with the colors produced. All readings should be made as soon as the solutions are poured over the papers, as the colors tend to change on standing.

An excellent series of buffers for this purpose may be prepared by following the directions published by Shohl and King,[1] or they may now be purchased ready for use in 100 cc portions from the La Motte Chemical Company of Baltimore. The buffers which will be found most useful are the following: 1.4, 1.6, 1.8, 2.0, 2.4, 3.0, which will cover the entire range from hyper to anacidity.

The following table gives the colors produced on the papers by gastric contents of different acidities together with the number of cubic centimeters of 0.1 N alkali which would be required to neutralize 100 cc of a solution of the hydrogen-ion concentration found, calculated on the assumption that all acidity in such solutions is due to hydrochloric acid.

Indicator.	pH.	Color.	Cc 0.1 N. NaoH required.	Remarks.
Töpfer's reagent	1.4	Deep red	44	Hyperacidity.
Töpfer's reagent	1.6	Reddish-orange	27	Normal acidity.
Töpfer's reagent	1.8	Orange	17	Normal acidity.
Töpfer's reagent	2.0	Yellowish-orange	10	Hypoacidity.
Thymol blue	2.0	Purple-red	10	Hypoacidity.
Thymol blue	2.4	Faint pink	4	Hypoacidity.
Thymol blue	3.0	Yellow	1	Anacidity.

We have used the procedure outlined above on a great variety of gastric specimens in which we have checked the findings by titration and by the use of the apparatus of Shohl and King.[1] We have also checked our results in a smaller number of cases by means of the electrometric method, and have used for this purpose a Leeds and Northrup potentiometer reading to 0.001 volts, an Epply standard cell, a calomel electrode of standard make, and a Clark electrode with shaker. Just before and just after each series of determinations we have checked our work by carrying out the process on a buffer of known pH content, in order to detect any poisoning of the electrode.

TABLE I.—COMPARISONS OF RESULTS OBTAINED BY DETERMINATIONS OF THE ACIDITY OF GASTRIC CONTENTS OF TEST PAPERS AND BY THE ELECTROMETRIC METHOD.

Specimen number.	pH by test papers.	pH by electrometric method.
1	1.3	1.27
2	1.4	1.40
3	1.4	1.32
4	1.5	1.56
5	1.6	1.64
6	1.6	1.53
7	1.7	1.75
8	1.7	1.80
9	2.0	1.95
10	2.3	2.38
11	2.5	2.43
12	2.7	2.65

As will be seen from the results presented above the agreement between the results obtained by the papers and by the electrometric method is astonishingly close, so that we feel justified in making the statement that after a little practice it should be possible to read these test papers to within 0.1 unit.

Summary. It is suggested that the customary titrations of gastric contents with Töpfer's solution be replaced, at least at the bedside or in the busy clinic, by the determination of the hydrogen-ion concentration by means of test papers, for which the only equipment needed is a small vial of these papers which may be carried in the pocket.

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PERNICIOUS ANEMIA IN ITS RELATIONSHIP TO SPRUE.*

A Preliminary Report.

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From the time of its first appearance in medical literature the position of sprue has been unique.[1] Throughout its whole history there have been able clinicians who have refused to recognize it as a distinct clinical entity and it must be admitted that there has been a reasonable basis for such an attitude. Its close similarity to pernicious anemia is a very old observation which seems destined to be repeated in every period. A study of the history of sprue shows that it was an old term before Addison's first report on pernicious anemia, having been accurately described by Hillary in Barbadoes in 1776. As early as 1737, John Brickell, M.D., in his "Natural History of North Carolina" mentioned "white flux" which undoubtedly was sprue.

It is interesting to note how infrequently sprue has been reported out of the tropics. This cannot be explained wholly on the ground of its being strictly a tropical disease because it has been observed repeatedly in this country in northern states among people who have never been in the tropics. Its recognition seems to depend in a measure, at least, on the personal equation of the observer. One experienced in tropical work would readily make such a diagnosis while one without this experience would fit the clinical picture of so-called sprue without reservation in an entirely different classification. An explanation of this state of things will be attempted later in this communication.

Points of Similarity between Sprue and Pernicious Anemia. Sprue first attracted attention in this country when pellagra appeared as a great scourge in the southern states in 1907. Up to that time it had been a rare term in American medical literature and when it did appear it was usually from the pen of some medical officer who had seen service in the Philippines or other tropical post. An exception to this general rule was the experience of Harris,[2] who found the disease in Georgia. In the South the diagnosis of "pellagra-sine-pellagra" was often made and an investigation not infrequently revealed the fact that the disease conformed to the description of sprue. Such confusion would likely never have existed had the blood-picture been considered. In pellagra there

* Read before the section on medicine of the Medical Society of North Carolina, Raleigh, April 15, 1924.

is no notable blood change while in sprue the rule is that the blood changes are usually as marked and as striking as in pernicious anemia. The term "pellagra-sine-pellagra" soon ceased to appear in the medical literature of the southern states, and justly so, for it became obvious quite soon in the experience with this disease that without the skin lesions or a very definite history of the past occurrence of such a condition the diagnosis was never justified. The diarrhea of sprue and the sore mouth also differed definitely from those conditions in pellagra and a consideration of these symptoms alone was quite enough for a differentiation.

Remissions seem by many to be regarded as not occurring in sprue but in reality they are fully as much a part of the disease picture in sprue as in pernicious anemia, if not, indeed, more so. These remissions are mentioned by all careful students of sprue. The writer has before him the record of one case of sprue diagnosed in 1915 and regarded as a typical case. There was no recurrence of symptoms in this case until 1923 though a careful follow-up correspondence had been applied throughout the whole intervening period. During these eight years there had occurred no symptoms. More recently a case diagnosed as sprue in 1916 returned to a colleague who now diagnoses pernicious anemia with full justification. In this case, however, there had occurred numerous recurrences and exacerbations.

The blood-picture in sprue is strikingly similar to that of pernicious anemia. The color index in every case observed by the writer at some stage of the disease has been over one. The usual range has been between 1.25 and 1.66 and the hemoglobin is frequently between 20 and 30 per cent. The morphology of the red blood cells has been much that of true Addisonian anemia in that there have been found the preponderance of oversized cells, poikilocytosis, anisocytosis, polychromatophilia and to a less extent the occurrence of nucleated red cells. The nucleated cells, as a rule, have been fewer and the occurrence of megaloblasts has been of less frequent record. It must be considered, however, that the search for these blood elements has not been routinely as thorough as in those cases regarded as pernicious anemia.

Among the important points of similarity between sprue and pernicious anemia is the Prussian blue reaction of Perl which occurs when sections of liver are brought in contact with a solution of potassium ferrocyanide and dilute hydrochloric acid. It occurs so infrequently in other conditions that its presence in obscure anemias has been regarded as strong evidence in favor of the pernicious type. It is noteworthy that it also occurs in sprue and in bronzed diabetes. Its occurrence is of more than passing note in this study for it seems to indicate that some hemolytic process has been active as the reaction depends on the presence of hemosiderosis resulting from the deposition of hemoglobin in the tissues after blood destruction.

Study of the bone marrow in sprue has been neglected, judging from the literature. This is true of all postmortem observations in this disease. Even Ashford has had few autopsy opportunities. The writer suspects that this may be explained by the victim of the disease coming to his death with another diagnosis. Bahr (Manson-Bahr)[3] describes the bone marrow changes in sprue and gives a table of comparisons between the two diseases. In sprue he found no increase in erythroblastic elements, while in pernicious anemia the characteristic changes were recorded. Very recently Bramwell[4] has stressed the similarity between the two diseases and thinks that Manson-Bahr's failure to find the evidences of erythroblastic response in the bone marrow in sprue needs further observation and corroboration. He thinks that it is highly probable that in sprue with blood changes so similar to those of pernicious anemia the same alterations in the bone marrow should be expected.

The lack of neurological changes in sprue has been regarded as a point of value in distinguishing between it and pernicious anemia. It is, of course, true that in sprue the nervous system suffers less frequently than in Addisonian anemia but it is an error to assume that it always escapes. The writer has records of a number of cases of so-called sprue which show indications of the usual cord changes of pernicious anemia. Among these cases should be cited that of a Virginia lady who had resided in Porto Rico continuously for eight years. During her last two years in Porto Rico she had been considered by the resident physicians as a case of sprue. Her story indicated for eight months before observation she had been annoyed with sensory disturbances in hands and feet and with some difficulty in walking. Examination revealed loss of sphincter control of both bowel and bladder, loss of the abdominal reflex, presence of the extensor plantar response (Babinski's sign) and exaggerated knee- and ankle-jerks. There was almost complete loss of appreciation of vibration sensation and marked diminution of tactile response in the lower half of her body. Ophthalmoscopic examination revealed old hemorrhagic areas. There were indications of a bulbar lesion affecting speech and deglutition. The diagnosis of subacute combined degeneration of the spinal cord was obvious. The blood showed a high-color index, all the variations in size, shape and staining reaction of pernicious anemia and also the presence of the megaloblast. To these findings was added achylia gastrica. In this case the type of sore tongue and the character of the diarrhea would have justified the diagnosis of sprue while a consideration of the whole case certainly justified the diagnosis of pernicious anemia. It could well be regarded as a typical case of sprue and, on the other hand, there was no single point against the diagnosis of pernicious anemia. One could but feel that the diagnosis was largely a matter of geography. In the tropics it would be called sprue, while out of the tropics it would be called pernicious

anemia. This is by no means an isolated instance of the difficulty and confusion surrounding the whole problem. As the writer's experience with sprue has grown he has become more and more impressed with the difficulty in making this differentiation. Cases seen in the past and diagnosed sprue are returning with every earmark of pernicious anemia, and to somewhat less extent the converse is also true. There are numerous cases in the sprue literature of the disease being complicated by pernicious anemia, of sprue developing into pernicious anemia and of the advanced stages partaking of the nature of pernicious anemia. Certain it is that the symptoms of the one have so merged into the other that a line of demarcation between the two in many instances cannot be drawn.

Achylia gastrica so frequently, if not universally, recorded in pernicious anemia has been regarded as offering a point of differentiation between it and sprue. It seems to be true that in sprue this condition does not occur so universally nor so early in the course of the disease, but the marked difference recorded in the literature is inexact for in sprue achylia does occur and probably much more frequently than one would infer. Its occurrence is later but the writer feels strongly that if the examination were repeated from time to time throughout the course of sprue the absence of free hydrochloric acid would be more frequently recorded. In a case in mind one year before the fatal termination free hydrochloric acid was present but it gradually diminished so that just before death it had disappeared entirely.

It would seem that in this day of laboratory dependence many of the valuable clinical observations of a previous generation are lost entirely or forgotten. One is struck in a review of the early records of pernicious anemia with the frequent references to mouth and intestinal symptoms. A sore mouth is by no means rare in pernicious anemia and the denuded condition of the tongue, the so-called "slick tongue," has been observed by even the casual attendant. The mouth symptoms of pernicious anemia were stressed by Lazarus[5] years ago. He recorded an extreme sensitiveness of the tongue, the hard palate and the gum. On examination he found on the tip and dorsum of the tongue and on the mucous membrane of the cheek circumscribed reddish areas of a mahogany color which varied in size from a mere point to a dime and which were extremely sensitive and represented areas of hemorrhage into the mucous membrane. In one case he recorded intense painfulness of the tongue and gums at the start of the disease, which lasted for three weeks and developed into severe salivation. This writer also mentions Ewald's observation of a case presenting round vesicles of pin-head size which developed on the tip of the tongue, on its inferior surface and on the mucous membrane of the lips and cheek which left behind a surface desquamated of epithelium. The observations of H. Müller and Laache are also noted in connec-

tion with the observation of excoriation extending in many cases throughout the whole length of the esophagus. One could almost as readily accept these observations as occurring in sprue as in pernicious anemia. Many of the earlier accounts of pernicious anemia are splendid accounts of sprue.

Recently the writer was consulted by two patients solely on account of sore mouth and tongue. Neither presented any other subjective complaint. In both there was an achylia gastrica and in both Ashford's Monilia psilosis was recovered. The neurological signs as well as the blood-picture justified a diagnosis of pernicious anemia, but the outstanding significant feature was sore mouth.

The close similarity between sprue and pernicious anemia is of considerable importance, being far more than a simple academic interest. Any investigator working with sprue who is familiar with the clinical manifestations of pernicious anemia must be constantly reminded of the close similarity and probable relationship. It all suggests the question, Is sprue a type of pernicious anemia? Regardless of the attitude one may assume in this matter, the fact remains that the clinician experienced in both conditions will repeatedly meet cases impossible of differentiation.

After this clinical experience it was only natural to apply Ashford's findings of the Monilia psilosis in sprue to the problem of pernicious anemia. The results to be recorded below hinge largely on how one regards the work of Ashford. Is the Monilia psilosis the cause of sprue or is it in any way connected with sprue? If the Monilia psilosis is accepted as the cause of sprue, the work here recorded becomes of great importance. If this work is not accepted, much remains to be done in determining the part the Monilia psilosis may play in pernicious anemia. It seems reasonable to assume that the occurrence of this organism in pernicious anemia is something more than a mere accident. Whether or not one accept sprue as a type of pernicious anemia is a matter of the smallest consequence, not at this time regarded as worthy of a controversy as the writer sees it. The evidence of the occurrence of the organism in pernicious anemia is presented as it is and further study and observation must determine its real significance.

Ashford's Monilia Psilosis in its Relation to Sprue. In 1901 Kohlbrugge[6] found in sprue in the intestinal mucus, in the lymphoid patches of the intestinal tract and in the epithelial covering of the esophagus and tongue great quantities of yeasts resembling Monilia (Oïdium) albicans.

In 1902 DeHaan[7] found the same yeast in both acid and alkaline stools.

In 1905 Van der Scheer[8] reported his inability to find the organism in tongue scrapings or gastric contents in two cases of sprue.

In 1908 LeDantec[9] found a yeast in sprue stools which would produce sprue symptoms in experimental animals, if a diarrhea was first established in some other way.

In 1909 Macy[10] reported finding a yeast in sprue stools in India. In 1913 Castellani and Low[11] described a number of yeasts which they isolated from sprue stools, but which they regarded as secondary invaders probably only playing the part of producing frothy stools.

The most important work up to 1914 on the part played by yeasts in sprue was that of Bahr (Manson-Bahr)[3] in that year. This report was the result of an exhaustive study made in Ceylon. It presents strong evidence for regarding sprue as a blastomycotic infection. Yeasts were found intracellularly in tongue scrapings during the attack, but not at any other time. These yeasts were the only organisms found in the deeper layers of the tongue. There was also found a general infection of yeasts in the intestinal mucosa in sprue, but in no other wasting diarrhea. It is stated that the relapsing nature, the chronicity and the latency are what one would expect from a knowledge of the life history of the blastomyces. This opinion was thought to be reinforced by a consideration of attenuated growth and recrudescences. This observer saw no reason for regarding the organism as any other than the thrush fungus.

Bahr's work was given a new impetus by Ashford,[12] working in Porto Rico. This latter observer spent a decade or longer in an exhaustive study of sprue in relation to a yeast which he named Monilia psilosis. It seems probable that this organism was the same that Bahr had studied in Ceylon, but it is not the Monilia albicans of thrush as so many seem to think. This organism produces on Sabouraud's medium round, yellowish, glistening colonies; it does not liquefy gelatin; it does not clot nor change the color of litmus milk; it usually produces gas in maltose, dextrose and levulose and occasionally in saccharose and galactose. Ashford will not accept an organism as of the species psilosis if it fails to produce gas with maltose. It never produces gas with lactose nor with mannite. The writer has found that if pure sugars are used invariably maltose, dextrose and levulose, and these only, will be fermented with liberation of gas. Until the highest purity sugars were used the results were most misleading. The writer has found it best to grow the organism at 30° C. Ordinarily at this temperature it requires forty-eight hours for a growth visible to the naked eye to appear. The exception to this rule occurs when the organism has been passed through an animal to increase virulence. In this instance the growth is usually more rapid. When colonies appear to the naked eye earlier than forty-eight hours after inoculation, it is reasonably safe to assume that they are not Monilia psilosis. Ashford emphasized the importance of an acid medium (as the original formula of Sabouraud designates) and used a +2 titer of decinormal sodium hydroxide with a phthalein indicator. The writer has modified this by making the titer +5 (10 cc of the medium

with a phthalein indicator will then require 5 cc of decinormal sodium hydroxide solution for neutralization). In addition to this decidedly increased acidity the writer has found that this acidity is much better produced with acetic acid than the more generally used hydrochloric acid. In this way the fluidity of the medium after sterilization is prevented and much costly material saved. Through a fortunate accident a batch of medium was burnt on the free flame after the addition of the sugar. It was soon learned that this medium was superior to that not so burnt. The caramelization so increased its good qualities that it is now intentionally resorted to in every instance by heating directly over the free flame. This is done until a definite brown color develops and the smell of burnt sugar is detected. The criterion of a good medium for the work in hand is that when feces is inoculated there will occur no growth on the acid agar-agar slant except of the higher forms and particularly the yeasts. The bacteria must all be completely inhibited and the medium can be so prepared that this can be accomplished without interfering in any way with the development of the yeasts. It has been found advantageous to use media of several degrees of acidity, in order to avoid the inhibition of any organisms which might be important for purposes of study. As a rule the best medium will titrate between +3 and +5 and this is the routine formula. It is expected that by the use of such a medium in general routine work many interesting fields will be opened up, especially in a group of bronchial affections which are non-tuberculous. The yeasts seem destined to play a conspicuous part in the medicine of the future. The development of a culture medium which grows them all readily with a definite inhibition of all bacteria is a step forward.

The Monilia Psilosis in Pernicious Anemia. As stated earlier it is a matter of small moment whether or not sprue is regarded as a type of pernicious anemia. The suspicion that such might be the case led the writer to study the occurrence of the Monilia psilosis in the latter disease and after that the graft became so much more important than the original study that this possibly controversial point is left to others more interested. Finding the Monilia psilosis in pernicious anemia shifted the scene entirely and relegated the whole subject of sprue to the background.

In 15 cases of pernicious anemia, the Monilia psilosis has been found in the feces. Of this numb there are only 2 cases about which there can be any diagnostic question and further study is necessary before the disease can be excluded. In something over 40 cases which were neither sprue nor pernicious anemia, the Monilia psilosis has not been recovered. In only 1 case of known pernicious anemia has there occurred any difficulty in growing the organism from the feces and this study was made during a period of remission. However, in this case the organism was readily grown

from the pyorrheal gums, a subject to be dealt with later. It has been notable that during remissions the organism is found with great difficulty or not at all in the feces. Speaking generally it can be stated that almost invariably the organism is found in the presence of the disease and equally certainly not found in its absence.

In numerous cases the Monilia psilosis has been obtained from cultures made from the gastric contents. It was suspected that possibly the absence of free hydrochloric acid might have been a contributing factor but this was disproved by finding the yeast in the gastric contents before the development of the usual achylia.

Feeding Experiments. In the feeding experiments no attempt was made to render the guinea-pig more susceptible by a faulty diet as had been done by Ashford following certain French investigators. Ashford employed some malted baby food. In the present work the organism was added to the animal's regular diet without any change in the usual manner of living. On the eighth day the first animal died. The source of the organism used was from the feces of a victim of pernicious anemia. Throughout the lungs of this animal were found a few isolated areas suggesting granulomata which seemed to conform with the "white spots" described by Ashford. The blood changes were quite notable in this case. The hemoglobin was reduced from 88 per cent to 62 per cent. There was a considerable preponderance of oversized red blood cells and a striking polychromatophilia. The one thing wanting was an excess of nucleated red cells. The marrow of the long bones presented an intensely red color in sharp contrast to the control animal's marrow. Care was taken to avoid the error of using young guinea-pigs because of the normally more decided red color of the marrow. In the marrow there was an excess of nucleated red cells and an apparent excess of myelocytes. The liver of this animal was sectioned and the Perl reaction applied and found decidedly positive. Again, this reaction was controlled by sections treated in the same manner from a normal guinea-pig. From the feces and gastric contents of the Monilia-fed pig the Monilia psilosis was recovered. It was notable that in none of the organs was a growth of the yeast obtainable.

The next guinea-pig was fed a Monilia psilosis from a case of suspected sprue occurring in the North Carolina Tuberculosis Sanatorium. This particular organism was sent to Colonel Ashford in Porto Rico for his examination and particularly for his opinion regarding the species. He has written that it is unquestionably the Monilia psilosis which he has found so universally in sprue. In every way the organism was true to type, which is not universally true of this class of yeasts. It produced gas in the fermentation tubes with maltose, levulose and dextrose. Litmus milk remained unchanged and gelatin was not liquefied. This organism was fed to a guinea-pig as a simple addition to its previous diet. For a time

no symptoms were produced and it was assumed that the organism from long incubator life had become attenuated. Consequently in order to render it more virulent passage through a rabbit was resorted to with death of the animal in forty-three hours after the intravenous inoculation. Autopsy of this rabbit revealed no gross changes, but the Monilia psilosis was recovered in pure culture from the liver, kidney stomach and feces. This new culture was then substituted for the old one and the feeding continued. After a few days the guinea-pig being thus fed died and the same changes that had been found in the first animal which had been fed a culture from the feces of pernicious anemia were again found. Notably the bone marrow of this animal showed great numbers of myelocytes chiefly of the neutrophilic variety and a definite excess of nucleated red cells. The color of the bone marrow was a brick-dust red, though it was from an old animal, and it was quite gelatinous in its consistency. The blood cells showed a very great variation in size with a marked excess of over-sized cells. There were definite variations in staining reactions and marked poikilocytosis. This animal showed the characteristic changes probably more definitely than did the former animal. In the lungs and liver there occurred a few of the granulomatous areas mentioned above and the changes generally were enough to justify the conclusion that the two processes were one and the same.

A third guinea-pig was fed a Monilia psilosis recovered from a fatal case of pernicious anemia. Until after the feeding had progressed several days, it was not known that this animal was pregnant. The feeding was discontinued until the young pigs were two weeks old, when it was resumed. In all six weeks feeding-time was required to cause death. Before death there was marked emaciation and loss of hair. At autopsy the bone marrow was deep red and gelatinous. The liver, and to less extent the kidneys showed a marked reaction to the Perl test. The cholesterol content of this animal's blood was 107 mg. per 100 cc of blood. The red blood cells showed definite megalocytosis and polychromatophilia. The young of this animal died a few days after the mother's death. These animals had not been fed the yeast, but had lived in the same case with the mother. Cultures from the intestinal tract of both the young animals showed the Monilia psilosis.

Intraperitoneal injections of the Monilia psilosis in white mice caused peritonitis but the tardiness of the onset of symptoms and recovery in some instances indicated that the animal was peculiarly resistant or else that the yeast was of low virulence.

All of the culture work on many animals fed this yeast showed that it was not a blood-stream invader except when injected intravenously. Given by mouth, it will eventually kill, but the time required varies greatly with different cultures, as would be expected. Growth on artificial culture media soon renders the organism less virulent and the longer the artificial growth the greater the loss in

virulence. The virulence is readily raised by passage through one or more animals. It seemed reasonable to assume from this work that the organism in the intestinal tract elaborated toxins which when absorbed prove to be hemolytic in nature.

The Monilia psilosis was next grown in dextrose water. The strength of the dextrose solution varied from 4 per cent to 20 per cent. The culture was incubated at 30° C. for five days and then filtered with great care to prevent any contamination. The filtrate was given intravenously to rabbits, after cultures had proven it to be sterile. The amount of the initial dose was 1 cc, which was repeated daily with a continuous increase in the size of the dose. The organism used in the first of this group of experiments intravenously had killed a rabbit in forty hours with a mycotic septicemia. The filtrate had no such effect. On the fifth day the rabbit receiving the filtrate was examined and the blood showed early changes. On the tenth day the blood showed numerous nucleated red cells which had formerly been absent and some of these cells were of the megaloblastic type. The hemoglobin was lowered 15 per cent. The red cells showed many variations in size and also poikilocytosis. The polychromatophilia present was of no significance for, as is well known, this is a normal finding in rabbit's blood. These blood changes could hardly be regarded as any other than those of a hemolytic anemia. After these definite changes had been produced the inoculations were discontinued and the animal's blood promptly returned to its original normal.

Source of the Monilia Psilosis in the Intestinal Tract. The question then arose, Where does this yeast come from and how does it reach the intestinal tract? Ashford in his sprue work in Porto Rico suspected the yeast-risen bread of the natives because from the center of the loaf he had secured cultures of the organism. This, however, could not explain the freedom from the disease in little children, who consume as much as or more bread than the adult. All of the available evidence strongly suggested that the organism was swallowed. After becoming satisfied that faulty cookery was not responsible for the infection, the writer reverted to the question of oral sepsis which W. Hunter had suggested in his work on the severest anemias. He had suspected a streptococcus as the cause, but this view had not been sustained. With this in mind, cultures were made from the gums in pyorrhea. The cases selected for this were victims either of sprue or pernicious anemia. Without difficulty the Monilia psilosis was readily grown and there has not occurred since that time a case of either of these two conditions in which there has been a failure to secure a growth of the organism from this source, except, of course, in those patients whose teeth have been removed and the gum has healed. It will be recalled that during periods of remission in pernicious anemia it has frequently been difficult, if not impossible, to secure a growth from the feces but from the gums the cultures have been consistently

positive. Cultures from the roots of extracted teeth at the time of removal have invariably proven negative. With a culture derived from the gums the hemolytic changes were produced when the filtrate was employed. Many controls of this gum work have been done and there are surprisingly few instances of a positive culture, regardless of the degree of pyorrhea existing. There have been some cases giving a positive response when there were no other evidences of disease, but this was to be expected. It would be as absurd to expect that every patient with the Monilia psilosis in the mouth was the victim of a grave blood disease as to regard every positive culture of a hemolytic streptococcus from the mouth as of clinical significance.

Summary. 1. The close similarity of pernicious anemia and sprue suggests the possibility of the two being types of the same condition.

2. Equally as readily in pernicious anemia as in sprue, the Monilia psilosis can be recovered from the feces, the gastric contents and the gums when pyorrhea exists.

3. The study of the yeasts is made extremely simple by the employment of a modification of Sabouraud's medium.

4. By feeding guinea-pigs with the Monilia psilosis a hemolytic anemia was produced. There were also produced changes in the liver and bone marrow which were suggestive of the action of a hemolytic poison.

5. A filtrate of the Monilia psilosis in dextrose water injected intravenously into rabbits caused blood changes apparently hemolytic in nature.

In conclusion the writer wishes to express to his friend, Dr. Thomas M. Green, his appreciation of his encouragement and kindly criticism. To Miss Lila W. Koonce, technician in the clinical laboratory of the James Walker Memoral Hospital, he offers his thanks for invaluable aid throughout the work.

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By George Draper, M.D.,
NEW YORK.

In 1915 I[1] published a series of cases of cerebrospinal syphilis which had been treated after the manner of Swift and Ellis,[2] over a period of from six months to two years. The results of this short course of treatment were most satisfactory, and may be found fully described in that original paper; but because this was a new method of treatment it was impossible to foretell what the subsequent results would be.

Ten years have now passed since those initial improvements were experienced by this group of patients, and it seemed that it would be not only interesting but instructive to observe what has happened since. Ten years is a long time through which to maintain satisfactory contact with a large group of patients and it is inevitable that a certain number should be lost sight of. This fact renders the absolute statistical value of such a review unsatisfactory. There are, however, enough observations available on this group of patients to be of value.

The material on which this communication is based may properly be divided into two portions. One, composed of the 25 which formed the original group reported in 1915, and the other later collection of 20 cases, which have been observed for a somewhat shorter period. Now, of the original group of 25, 9 or 36 per cent have disappeared; 7, or 20.8 per cent are dead; 9 or 36 per cent are living, practically in almost all cases free from symptoms and with 2 exceptions actively at work. One of the individuals who is not actively at work is physically and mentally quite capable of working but, without the pressure of necessity, prefers to remain inactive.

The following table shows the detail of the spinal fluid and serological formula of each case at the time of admission to treatment, at the time of discharge at the end of treatment, and again at the end of the ten-year period. A perusal of the table will show that the gain achieved at the end of the treatment period has in all cases not only been held but in numerous instances to a surprising degree has been bettered. Such physical signs as the Argyl-Robertson pupil, absent reflexes, and marked disturbances of skin sensation have not changed, perhaps because such signs depend on actual destruction of nerve tissue. But the subjective symptoms, such as pain, gastric distress, weakness and, especially, irritability and lack of mental poise have improved during the six to nine years

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Case No.	Diagnostic data.								Discharge data.						
	Spinal fluid.				Blood W.R.	Duration of treatment, mos.	Number of intravenous.	Number of intraspinal.	Spinal fluid.				Blood W.R.	Condition.	
	Cells.	Glob.	W.R.	Gold.					Cells.	Glob.	W.R.	Gold.			
49	25	±	0.5 −	0	−	9	10	0	1	−-±	0.5 −	0	−	Marked improvement; fixed pupils K. J. −	
126	138	+	0.1 ++++	0	++	4	9	5	0	++	0.5 +++	1233-2100	±	Gastric crises stopped; general improvement; fixed pupils K. J. −	
76	40	+	0.3 ±	0	+++	5	17	5	1.2	±-+	0.5 +	0	++	Pain gone; ataxia better; fixed pupils K. J. −	
95	51	+	0.5 ++	0	Not done	7	21	3	10	++	0.5 +++	0	−	Ataxia-irritability; pupils sluggish K. J. −	
96	133	+++	0.3 +++	0	+++	3	10	5	6	++	−	0	−	Slight improvement; complete ataxia K. J. −	
91	53	+	0.5 +	0	−	6½	10	0	15	±-+	−	0	−	Improvement in visual field and general health.	
22	52	+++	0.3 ++	0	++	9	24	12	10	−	0.5 ±	1112-161	−	Patient apparently well.	
18	40	++	0.1 +++	0	+++	4	11	9	23	−	0.5 ++	0	++	Patient apparently well.	
25	327	+++	0.5 +++	0	+++	9	22	15	33	++	0.3 +++	0	+++	Marked improvement in all symptoms.	

Ten-year data.

Case No.	Spinal fluid.				Blood W.R.	Condition.	Time, yrs.	Without symptoms.
	Cells.	Glob.	W.R.	Gold.				
49	...	...	...	...	...	No pain at all; fixed pupils K. J. –	6	Well; active.
126	2	+	2.0 –	112321000	–	Complete subjective comfort and efficiency; fixed pupils K. J. –	8	Mercury and 7 Ogilvie intraspinous; well; active; severe arsenic dermatitis.
76		Patient refused puncture				Continued absence of pain; ataxia slight; pupils and K. J. same	9	Comfortable; not active.
95	3	0	2.0 ±	11121100	–	Ataxia improved; irritability gone; physical signs the same	6½	Well; slight ataxia; active.
96		Patient not available				Ataxia improved; bladder control less good; general condition excellent	8	Feels well; very ataxic.
91		Patient refused puncture				Held eye gain; fine general health	8	Eyes stationary; well; active.
22	3	–	–	343321000	–	Patient apparently well	8	Well; active.
18	0	–	–	...	–	Patient apparently well	8	Perfectly well; active.
25	2	–	–	1222100	–	Continued improvement in strength and psychic poise	9	Well; active.

in which these patients have lived without treatment. Two or 3 of the cases, it is true, have received, about midway between the cessation of the original series of injections and the present, a short course of treatment. But several who have received nothing have steadily improved in physical well-being and psychic demeanor.

In the original communication the cases were arranged according to their outstanding symptoms. Thus there was a pain group, an ataxia group, an optic atrophy group, a single case of cranial nerve nucleus involvement, and the psychic disturbance group. Of the 9 cases who have done well, 3 were from the painful group, 2 from the ataxic, 1 from the optic atrophy, the bulbar case, and 2 from the psychic group. In the original spinal fluids the cell counts of these 9 cases ran from 25 cells to 327 per 1 cm. At the end of treatment the cells varied from 0 to 33 cm. and at the end of the ten-year period from 0. to 3. The Wassermann reaction, which was strongly positive in all the fluids at the start and which at the end of treatment was not completely negative, at the end of the ten-year period was negative throughout. The globulin reaction followed a similar course. No colloidal-gold reaction was done on the original fluid because the test had not been devised at that time, so that while in a few instances, subsequently, fluids from this series were tested by the Lange method, the observations are not sufficiently consistent to warrant a comparative report. It may be said, however, that in the ten-year spinal fluids the gold reaction shows a very slight change of the luetic type in all the fluids examined. The blood Wassermann reaction was strongly positive in the original test, incompletely eliminated at the end of treatment, but at the end of ten years was negative in every one. Obviously, then, there has been during these intervening years a continued improvement, not only in the physical well-being and relief from pain and specific disability, but also an almost complete clearing up of the disturbed formulæ.

Before entering upon a discussion of the inferences to be drawn from these results, it would seem desirable to consider for a moment the other group of 20 cases which have been treated in precisely the same way and during almost as long a period. Of these 6 or 30 per cent have disappeared, 2 or 10 per cent are dead, 7 or 35 per cent are well and active, 5 or 25 per cent are worse. Of these last 3 turned paretic during or after months of treatment; 1 was already a fully developed paretic when treatment was begun and 1 was an extremely painful ataxic who after a long period of amelioration went steadily and rapidly down hill. Thus it appears that the number of those who are able to be comfortable and work actively is practically the same in each group. But in this last group there are certain striking individual cases which are so important for the purpose of rounding out my conception of the therapeutics of this disease that it is necessary to give brief histories of them. Three of

them represent failures; 1 a questionable or perhaps accidental success.

CASE I.—W. T. C., male, telegrapher, aged fifty-two years, complained chiefly of loss of vision. In November, 1916, the patient could see enough to work but his visual fields were very much contracted. There were absolutely no other symptoms or signs. His spinal fluid formula at that time showed 6 cells, globulin 1 plus, Wassermann reaction positive in 0.1 cc, gold-chloride reaction 5555554210. The patient received 15 intravenous injections and 10 intraspinous up to February, 1918. His eyes held their own during this period. He then went without treatment, apparently perfectly well until the summer of 1922, when without warning he suddenly developed active paresis. His spinal fluid showed precisely the same formula as it had in November, 1916. This case is particularly striking because of the absence of any mental or bodily symptoms or signs save the localized optic atrophy.

CASE II.—W. C. C., lawyer, aged forty-six years, complained chiefly of numbness over the buttocks, through the crotch, and down the backs of the thighs. The spinal fluid formula was: 41 cells, globulin 4+, Wassermann reaction 4+ in 0.3 cc. Treatment was begun in February, 1915. At the end of the first year, the patient had received 29 intravenous injections of salvarsan and 14 intraspinous injections of serum, as well as a considerable number of injections of mercury. The spinal fluid formula at this period showed 3 cells, globulin 1+, Wassermann reaction 3+ in 1 cc. Gold chloride 111332000. The subjective symptoms were practically gone, patient felt and seemed perfectly well. During the next nine months, however, he received 2 more intraspinal treatments and in October, 1917, the fluid had relapsed, showing 45 cells, Wassermann positive in 0.4 cc; gold reaction 22342100. The patient was then given 4 intravenous treatments and 10 intraspinous, after which the spinal fluid showed a gold curve of 5554421000. Nevertheless he remained well all through the summer of 1918. In January, 1919, he was still free from clinical symptoms but the spinal fluid showed 30 cells, globulin 3+, Wassermann reaction positive in 0.4 cc and a Lange test of 5555443210. He received 3 intravenous and 4 intraspinous injections which was followed by a general improvement in health throughout the year. Beginning in February, 1920, he received 5 intravenous treatments each followed by a spinal puncture but no injection of serum. At the end of this course the spinal fluid still showed 33 cells, 3 plus globulin, a complete fixation in 0.4 cc and a gold curve of 5555554211. Shortly after this spinal fluid formula appeared, the patient expressed great worry lest he lose his mind. He was reassured with the statement that people who were in fear of losing their minds rarely did so and

at all events never themselves recognized the moment of mental change. He expressed particular worry over the fact that he could not sleep and that the loss of sleep was pulling him down. Two weeks later he said to me with just a suggestion of exaggeration in his tone, "Well, now I am perfectly all right; I am not sleeping at all, but I am so well that it does not make any difference. I feel splendidly." The subtle change had taken place. The euphoria of clinical paresis had begun. The point of particular interest about this case is the steady advance of the disease in the face of prolonged and vigorous treatment.

Case III.—M. B., jeweler, aged thirty-two years, complained only of incessant headache.

In May, 1914, the patient is reported to have had a cell count in the spinal fluid of 500, but the first fluid in this series of observations showed 11 cells, globulin 2+, and Wassermann reaction 3+ in 0.3 cc. No gold reaction was done at that time. The patient was given 21 intravenous and 14 intraspinous injections with some temporary relief from the headaches. Another series of 18 intravenous and 10 intraspinous produced a very considerable relief from the headaches and the last spinal fluid showed 13 cells, negative Wassermann reaction, but a gold-chloride curve of 223321000. Again after a short period his headaches began again. Two years later he became paretic.

These 3 cases illustrate the interesting condition in which individuals complain of a single rather isolated symptom. Except for this one disability, they had no other somatic or psychic indication of the disease. They all showed spinal fluid and serum changes. In the face of the most intensive and prolonged treatment all three turned paretic.

Case IV.—G. A., aged forty-one years, a business manager, came for advice because he was worried lest he develop locomotor ataxia having been treated for syphilis many years ago. There are no physical signs indicative of central nervous disease, the patient has a perfectly clear and well poised psyche, and has no symptoms. The blood Wassermann reaction was 4+; spinal fluid cells, 105; globulin, 3+; Wassermann, 4+ in 0.4 cc; gold reaction, 553421000. During the last two months of 1916 and for the first six months of 1917 the patient received mercury injections, salvarsan injections and a few intraspinous injections. At the end of this period his cell count was 7 cells, Wassermann was positive in 0.4 cc, and the gold curve was 5334421000. The patient then appeared to be as well as ever and did not return for any treatment until 1922 when he came back in response to a follow-up letter. He appeared to be in perfect health in every respect with the possible exception of getting tired more easily than in the past. There were no physical

signs indicating central nervous disease. The spinal fluid showed 102 cells, positive globulin, Wassermann in 0.4 cc, and Lange curve 123444210. The patient was immediately put on a course of treatment and during the past eleven months has had 30 intravenous injections and 13 intraspinal. His spinal fluid today shows 1 cell, negative globulin, Wassermann incomplete fixation in 2 cc and Lange gold curve 1112332100. The patient is still without symptoms.

Here then is an individual who presented eight years ago the interesting paradox of complete freedom from any signs or symptoms of central nervous system disturbance in the presence of a fully developed paretic formula in the spinal fluid and blood. Under treatment the spinal fluid formula was very definitely modified toward the normal, but without any apparent effect upon the patient's general health which remained as good as it had been before. Then, after a period of four years without treatment and while feeling practically well, the patient returned with a fairly active syphilitic meningitis spinal fluid formula. If it had not been for the follow-up letter, this patient would undoubtedly have gone on indefinitely without consulting a doctor. In view of this finding, it is interesting to speculate as to what has become of the 9 disappeared cases in the first group and the 6 disappeared cases of the second group. One cannot escape the thought that some of these individuals likewise may have developed a rapidly advancing paresis or syphilitic meningitis at the end of a two- or three-year period of apparently good health.

Now, if we consider all this material together two fundamental facts appear. One is, the difference in the severity of the disease expressed usually in terms of disproportion or lack of relationship between clinical symptoms and serological changes. The other is the different manner in which various individuals respond to treatment. If salvarsan and salvarsanated serum are specifics they should cure every time, unless there be another factor involved. The obvious inference from these observations is that the factor which determines the differences in intensity of the disease and the differences in response to therapy is one and the same, namely, the variable factor of individual constitution. There is undoubtedly still a third but minor influence present and that is the period in the disease at which the case appears for treatment. Obviously, then, the ideal therapeutic combination for the treatment of cerebrospinal syphilis is that of a specific spirocheticide and a specific resistance elevator. So much has been written about the specific spirocheticides that it would seem unnecessary to discuss them again at this time, but it may be worth while to consider for a few moments the possibilities that exist for raising to a higher level the specific resistance of the individual.

There are many observations recorded by clinicians of every age

concerning the relationship of certain types of mankind to certain diseases. Nacké[3] pointed out some sixty or seventy years ago that individuals who developed locomotor ataxia belonged to what he called the "hoch wuchs," asthentic type, whereas the paretic was a "breit wuchs" or thick set, broad-faced individual. In 1917 I reported a series of cases of cerebrospinal syphilitics studied from the standpoint of their body conformation and found the same situation as that described by Nacké. Such observations as these lend support to the conception of specific resistance-lacks. These specific resistance-lacks must undoubtedly depend upon characters in the individual constitution. Without entering at this time upon a discussion as to the mechanism which determines the constitutional differences in human beings, we may properly recognize the fact that attempts have been made throughout the history of medicine to correct these inadequacies of resistance. The simplest example of this sort of therapeutics is the fresh air, overfeeding and rest treatment of tuberculosis. But there have been other, much less obvious, and indeed totally unexplained phenomena of resistance elevation, often as a result of the most unexpected influence. Perhaps one of the most spectacular of these was the effect of erysipelas and the bacillus prodigiosus in raising the resistance in certain forms of sarcoma as pointed out by Coley.[4] The recent much talked of cure of paresis by inoculation with living malaria germs may very well be another example of this sort. The new pentavalent arsenical "tryparsamide," which was employed so successfully by Louise Pearce[5] in African sleeping sickness, in all probability, influences the disease beneficially through its effect on the constitution of the individual.

To anyone who has had the opportunity of observing the extraordinary change in general health and indeed of the entire personality which occurred in the cases of the first group of this series, it must become apparent that the change in the individual goes far beyond the simple return to a symptom-free state due to the destruction of the spirochete.

Conclusion. The Swift-Ellis method of treatment undoubtedly is very effective in a certain type of case, representing, according to this small but varied series, about 36 per cent of all cases of cerebrospinal, or central nervous syphilis.

Successful results of the treatment of cerebrospinal syphilis do not depend alone upon the spirocheticidal effect of salvarsan and mercury, there is undoubtedly some other factor developed in the course of the treatment, which successfully raises the resistance of the individual. When this resistance elevator fails to develop, no amount or intensity of treatment with salvarsan, serum and mercury can check the destructive advance of the disease.

In view of the tendency to recrudescence, all apparently cured

cases should be instructed to report for physical examination and spinal fluid test every two years and possibly oftener.

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VOLUME AND COMPOSITION OF THE BLOOD IN ADDISON'S DISEASE.

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Addison, in his original description of the constitutional and local effects of disease of the suprarenal capsules, called attention to the following characteristic features of this condition: "anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of color in the skin." At the time these observations were made, quantitative methods for the estimation of the hemoglobin and erythrocytes were not available. The appearance of the skin and mucous membranes in many cases is such that a severe grade of anemia is often suggested, particularly in blond persons and in those with a mild degree of pigmentation, which gives the skin a light brownish sallow tint. In other cases, there is no suggestion of anemia because of the extreme degree of pigmentation, although the mucous membranes, by contrast, appear to be paler than normal. Since Addison's complete description of this interesting condition appeared, numerous observations have been made, both from the clinical and laboratory standpoints. The question of the blood findings has been considered by a number of workers, with some diversity of opinion relative to the existence of anemia. The comparative rarity of this disease may explain this fact in some degree.

Literature Relating to Composition of the Blood. Averbeck[2] asserts that anemia is present with a reduction of the total blood volume, which masks the exact degree of anemia. Buhl[4] holds that there is a quite uniform, sharp decrease of blood cells, while Tschirkoff[17] made interesting observations in 2 cases in which he noted a daily fluctuation in the whole amount of hemoglobin, as well

as the proportion of oxyhemoglobin to reduced hemoglobin. Neumann[10] observed 1 case in the acute stage of Addison's disease in which low erythrocyte values (1,120,000 for each cubic millimeter) were obtained. Following clinical improvement, a progressive increase in erythrocytes was observed. Nothnagel[11, 12] believes that anemia is not a primary symptom of Addison's disease. He found average normal hemoglobin and erythrocyte values in uncomplicated cases. Hamel[8] says that in cases of Addison's disease with anemia and morphologically normal blood, tuberculosis of the suprarenals is probably associated. If anemia is accompanied by morphologically disturbed blood, carcinoma of the adrenal should be suspected. Dock[6] found average normal blood values in 4 cases, and concludes that anemia is not an essential feature of Addison's disease. Osler[13] says that anemia is not common, the blood counts being normal in the majority of cases. Several observers have called attention to a high relative lymphocytosis in this condition, to which finding a prognostic value was assigned.

On account of this diversity of opinion with regard to the incidence of anemia in Addison's disease, and since a rather large number of cases had been observed in the Mayo Clinic during the last two years, it was considered advisable to study the blood findings in these cases. It seemed possible that many of the diverse quantitative data with regard to the blood, noted by different observers, might be explained on the basis of fluctuations in the blood volume; therefore, the percentage hemoglobin and erythrocyte counts were correlated with the blood-volume values obtained by a method of reasonable clinical accuracy.

Seventeen cases of Addison's disease, all typical except one (Case XVII), were studied.* Three cases came to necropsy when definite lesions of the suprarenal glands were found. Case XVII presented features of unusual interest. The patient had syphilis, and, following arsphenamin injections, a group of symptoms developed closely approaching that observed in true Addison's disease: asthenia, low blood-pressure, and definite pigmentation. The pigmentation was especially noticeable on the tongue and mucous membranes of the mouth. Following the Muirhead treatment, as outlined by Rowntree,[15] marked improvement followed, which has persisted for two years. The exact status of this case is not quite clear. We believe that disease of the suprarenals existed in which compensation was disturbed by the arsenical treatment. A syphilitic lesion of the suprarenal bodies was suspected.

Terminology. There is no group of terms which designates the various states of blood volume and the different cell-plasma-volume ratios. To supply this need, the following terms have been suggested:[3] Normovolemia for normal blood volume, hypervolemia

* The study of the blood in this series of cases, correlated closely with the data in a larger series reported from the Main Clinic.[16]

for increased blood volume, and hypovolemia for decreased blood volume. To designate the different cell-plasma-volume ratios, the following qualifying terms may be used as prefixes: Simple for normal cell to plasma-volume ratio, polycythemic for increased cell to plasma-volume ratio, and oligocythemic for decreased cell to plasma-volume ratio.

Treatment. In 11 cases the full Muirhead treatment was used. In Cases VI, XV and XVI, in which a shock-like state was present, the treatment consisted of forced fluids, glucose and stimulants. There was a marked intolerance to the treatment with epinephrin in Case VI.

Findings. The hemoglobin was 70 per cent by the standard Dare method, and 90 per cent or less by the Haldane-Palmer method, and the erythrocytes numbered 4,000,000 for each cubic millimeter or less in 6 cases (37 per cent, Table I). There was borderline anemia in 2 cases. The patient in Case IX, who had the most marked degree of anemia, died within three days. Four of the 6 patients in whom the anemia was fairly definite died within a month. Except in Case IX the anemia, when present, was mild. There were no instances in which there was a high percentage of hemoglobin or high cell counts except in Case VI, during the shock period of acute suprarenal insufficiency. Subsequent examination of the blood showed this to be transient and definitely associated with the shock condition. Considerable variations in hemoglobin and erythrocyte values, seemingly too great for errors of method, were observed in several cases for short periods. The repeated volume studies in several cases seem to show that the percentage hemoglobin variations may be related to shifts in plasma and cell volumes.

Volume and Hemoglobin of Erythrocytes. The volume index of Capps,[5] or volume of the red cells as compared with normal, and the saturation index of Haden,[7] or relative amount of hemoglobin in the cell as compared with normal, were determined in 5 cases. The color index, average volume of the erythrocytes and hemoglobin content of individual cells is shown in Table II. The hemoglobin values are expressed in percentages according to Haldane's and Haden's normal standards, 13.8 and 15.6 gm. of hemoglobin for each 100 cc of blood for both sexes, respectively. The normal color, volume and saturation indexes are 1. The normal volume of the average cell, according to Haden, is 9.2×10^{-11} cc. The average normal hemoglobin content of the average cell in both sexes is 3.12×10^{-11} gm. The actual percentage of hemoglobin in the average erythrocyte is 33.9. In this series of cases of Addison's disease, the color index was less than 1 in 3 instances, the average being 0.9. The volume index was 1 or less in all cases. In Case III, a volume index of 0.78 with hemoglobin of 105 per cent was observed. In Case V a volume index of 0.82 was found with a percentage of

TABLE I.—BLOOD STUDIES IN ADDISON'S DISEASE.

Case.	Date.	Hemoglobin per cent.		Erythrocytes.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Transitionals, per cent.	Eosinophils, per cent.	Basophils, per cent.	Remarks.
		Dare.*	Palmer									
1 (A 403755)	9- 8-22	70	64	4,000,000	6,000	....	....	...	...	...	...	Typical case; patient improved.
	9-18-22	73	72	4,380,000	11,200							
2 (A 401101)	8-12-22	80	105	4,700,000	8,700	48.0	34.5	4.5	5.0	6.0	1.5	Typical; patient much improved.
3 (A 407966)	10-17-22	75	105	4,610,000	7,200	52.0	39.0	2.0	3.0	4.0	...	Typical.
4 (A 59466)	4-21-23	77	...	4,980,000	8,700	58.5	24.5	4.5	5.0	6.0	1.5	Typical; patient much improved.
	4-24-23	80	111	5,070,000	6,000							
5 (A 433553)	7-19-23	67	...	3,750,000	....	36.0	54.5	1.5	3.5	4.0	0.5	Typical; patient died one month later.
	8-15-23	69	82	3,920,000	5,200	25.0	62.5	5.8	2.5	4.0	0.5	
6 (A 291269)	7- 3-23	78	...	5,260,000	8,900	64.0	30.0	3.0	1.0	1.0	1.0	Clinically typical; patient died seven days later. Necropsy revealed chronic caseous tuberculosis of suprarenals and lungs.
	7-13-23	..	154									
	7-15-23	85	112	5,440,000	During shock period							
7 (A 426922)	5-22-23	..	104	.....	7,600	....	....	...	...	...	...	Clinically typical; patient died twenty days later. Necropsy revealed marked suprarenal atrophy. Old tuberculous pleuritis.
	5-28-23	78	...	4,880,000	7,200							
	5-30-23	78	111	4,850,000	7,200							
	6- 7-23	78	119	4,850,000								
8 (A 232618)	7-17-20	..	...	.....	....	48.5	46.7	3.0	...	1.0	1.0	Clinically typical. Chronic tuberculosis of kidneys. Patient died six months later.
	7-31-20	68	...	4,380,000	7,600							
	8- 2-20	76	...	5,100,000	9,200							
9 (A 411539)	11-29-22	53	...	3,280,000	8,600	46.5	30.5	4.5	...	3.8	3.0	Patient died three days later. No necropsy.
	12- 1-22	50	...	2,960,000	6,400	60.5	30.5	4.5	2.0	1.5	1.0	
10 (A 390936)	5- 9-22	70	...	4,090,000	17,100	64.0	26.0	2.0	4.0	3.0	...	Typical case; patient died one month later.
11 (A 352505)	3-15-21	67	...	4,020,000	13,800	40.0	52.0	3.5	...	2.5	1.0	Clinically typical. Necropsy revealed bilateral tuberculosis of both suprarenals.
	2-26-22	68	...	3,950,000	12,400	40.5	43.5	8.0	...	6.0	2.0	
12 (A 428040)	6- 6-23	76	...	4,440,000	8,000	51.5	40.0	2.0	...	3.5	2.5	Typical; patient improved.
	6- 7-23	76	101	4,440,000								
13 (A 400254)	8-16-23	67	77	4,210,000	11,300	49.5	45.0	1.0	2.5	2.0	...	Typical.
	8-23-23	73	...	4,280,000	13,800							
14 (A 385612)	3- 7-22	71	...	4,040,000	6,800	42.5	50.0	4.5	...	2.5	...	Typical; patient died one year later.
	.....	71	...	.....	....	40.2	54.0	2.0	1.0	2.5		
15 (A 458373)	3-14-24	75	106	4,830,000	10,000	34.5	59.0	1.0	2.5	2.5	0.5	Typical.
	3-22-24	75	106	3,920,000	9,200	52.0	46.0	...	2.0			
16 (A 459172)	3-21-24	72	92	4,690,000	6,600	70.0	28.0	2.0	...	...	...	Typical; patient died April 8, 1924.
Average values	.....	72	100	4,420,000	9,040	48.0	40.5	3.2	2.8	3.2	1.7	

* Standard: Dare.

TABLE II.—VOLUME AND HEMOGLOBIN CONTENT OF THE ERYTHROCYTES.

Case.	Erythrocytes.	Hemoglobin.			Hematocrit cells, per cent.	Color index.*	Volume index.*	Saturation index.*	Volume average cells in cc $\times 10^{-11}$	Gm. hemoglobin in average cell $\times 10^{-11}$	Actual per cent hemoglobin in cells.
		Gm. for each 100 cc of blood.	Normal, per cent.								
			Haldane scale.	Haden scale.							
1	4,000,000	8.8	64	57	33	0.7+	0.98	0.73	8.25	2.21	26.7
2	4,700,000	14.5	105	93	43	0.1	1.08	0.91	9.15	3.08	33.5
3	4,610,000	14.5	105	93	30	1.0	0.78	1.29	6.50	3.10	47.0
5	3,920,000	11.3	82	73	27	0.9	0.82	1.13	6.90	2.80	40.0
7	4,850,000	15.3	111	98	41	1.0	1.00	1.01	8.40	3.10	37.0
Average	4,410,000	12.8	93	82	35	0.9	0.93	1.01	7.80	2.80	37.0

* Based on Haden's normal hemoglobin standard.

hemoglobin of 82. The average volume index for the 5 cases was 0.93. The saturation index was less than 1 in Cases I and II, while the average for the group was 1.01. The average volume of the individual erythrocyte was decreased in Cases III and V, and the average volume for the group was 7.8×10^{-11} cc. The average content of hemoglobin in the cell was 2.8×10^{-11} gm. while the percentage of actual hemoglobin for each cell was 37.

According to these calculations, the red cells in 5 cases of Addison's disease showed a decreased cell volume with an increased saturation index as compared with Haden's values, and increased percentage of hemoglobin for each cell. In Cases III and V the relatively high percentage of hemoglobin with relatively low percentage of cells by hematocrit can be explained by a small cell volume with high content of hemoglobin.

Leukocytes. There were no striking variations in the number of leukocytes for each cubic millimeter of blood. Mild leukocytosis was present in 5 cases; in the remainder the counts were fairly normal. The average for the entire series was 9,040 for each centimeter of blood. The differential formulas verify previous observations on the presence of a relatively high lymphocytosis. In this series, the relative value of lymphocytes was increased in 11 cases or 68 per cent, the average percentage value for the entire group being 40.5. In no instances were low relative values found. The relative lymphocyte counts apparently had no prognostic value. The polymorphonuclear cells were relatively decreased in every case, the average values for the series being 48 per cent.

Blood and Plasma Volumes. Blood-volume changes in Addison's disease have been suggested as a possible explanation for the absence of anemia. It is conceivable that an actual decrease in the circulating hemoglobin or erythrocytes might be partially masked by a shrinkage in the total blood volume. Percentage hemoglobin values would not accurately reflect the true condition. With this point in mind, volume determinations were made by the dye method in a series of 9 cases in which the clinical diagnosis was Addison's disease. According to body weight, the total circulating blood volume revealed normal relative values, normovolemia (Table III) in 8 cases. In 1 case (Case V) there was decreased relative blood volume, but it was still within the normal range. In Case II, with average body weight, a high normal total blood volume was found, with a normal cell-plasma-volume ratio by hematocrit. In Case XVII, during the period of suprarenal insufficiency there was a slightly increased total blood volume according to body weight, but a decreased cell-plasma volume ratio according to hematrocrit or oligocythemic hypervolemia. Determinations made eight months later during the period of improvement showed a simple normovolemia. When calculated on the basis of surface area, the relative volume values reveal practically the same degree of variation with regard to area as to weight in the entire series.

TABLE III.—BLOOD AND PLASMA VOLUME DATA IN ADDISON'S DISEASE.

Case.	Date.	Sex.	Age, years.	Weight, kg.	Height, cm.	Surface area, sq. m.	Blood volume.			Plasma volume.			Hematocrit, cells, per cent.	Hemoglobin, Haldane-Palmer, per cent.	Clinical condition.
							Total, cc.	Cc. for each kg.	Cc. for each sq. m.	Total, cc.	Cc. for each kg.	Cc. for each sq. m.			
1 (A 403755)	9–14–22	M.	53	52	165	1.59	4260	82	2660	2860	53	2530	33	64 72	Improved.
2 (A 401101)	.....	M.	26	62	177	1.79	6240	100	3480	3550	57	1970	43	105	Markedly improved.
3 (A 407966)	.....	M.	42	50	172	1.57	3920	78	2500	2740	55	1750	30	105	Improved slightly.
4 (A 59466)	5– 3–23	M.	50	58	188	1.75	4710	81	2700	2940	51	1680	39	111	Poor.
	8– 1–23	..	..	64	188	1.87	5820	91	3300	3620	57	2060	38	103	Improved.
	2–26–24	..	..	63	188	1.84	6120	97	3320	3850	61	2100	37	113	Improved markedly.
5 (A 433553)	.....	F.	58	39	154	1.32	2900	75	2200	2120	55	1590	27	82	Poor. Died twenty days later.
6 (A 291269)	.....	M.	53	52	170	1.71	4000	77	2340	2320	45	1360	42	112	Definite shock.
7 (A 426922)	6– 7–23	M.	31	65	173	1.79	5330	82	3000	3145	48	1750	41	119	Mild shock, poor condition.
15 (A 458373)	3–24–24	M.	24	59	170	1.65	4750	80	2880	3240	55	1950	32	106	Mild shock.
	5– 9–24	..	..	59	170	1.65	4940	83	3050	3210	54	1930	35	106	Slightly improved.
17 (A 387986)	9–15–23	M.	37	60	175	1.75	6270	104	3580	3760	63	2150	30	97	Improved.
	4– 3–24	..	..	60	175	1.75	4980	83	2850	3330	55	1900	33	110	Good.
Average	.....	..	..	57	170	1.70	4940	93	3180	3120	54	1890	32	108	

In Case IV, three determinations of the blood and plasma volume were made within an observation period of sixteen months. The first was made during a period of marked suprarenal insufficiency in which simple normovolemia existed. The percentage hemoglobin was 111. The second determination was made four months later, when definite clinical improvement had taken place. The total blood volume had increased 1100 cc (23 per cent), the plasma volume being increased 680 cc and the cell volume 400 cc. The actual circulating hemoglobin* had increased 105 gm. (14 per cent), while the percentage hemoglobin was 103, a decrease of 7 per cent. The increase in total blood volume explains this discrepancy. This would indicate a dilution phenomenon plus hemoglobin increase, in which the percentage of hemoglobin does not reflect actual hemoglobin increase because of augmentation of total volume. The third determination, nine months later, revealed a slight increase in total blood volume, 300 cc (5 per cent), which was practically all plasma volume. Study of this case would seem to indicate that, during the period of suprarenal insufficiency the volumes were decreased, with restoration of water and hemoglobin during the recovery period. The relation of blood volume to body weight was within the normal range in all three determinations, in spite of an increase in weight of 5 kg.

TABLE IV. NORMAL VALUES IN FIFTY CASES[1*]

	Range.	Average.
Blood water, per cent	79–83	81
Plasma water, per cent	91–93	92
Cell water, per cent	60–68	64
Blood volume, † total circulating, cc	4930–7430	6180
For each kilogram of body weight, cc	72–100‡	86
For each square meter of surface area	2550–4000	3360
Plasma volume, † total circulating, cc	2960–4160	3610
For each kilogram of body weight, cc	43–59	53
For each square meter of surface area	1420–2250	2050
Cell volume in cc, total circulating	1970–3310	2550
Hematocrit cells, per cent	38–45	40

Author.	Determinations.	Hemoglobin, gm. for each 100 cc. Males.	Females.
Lichtenstern	61	14.14	13.10
Williamson	900	16.60	15.55
Haldane and Smith	12	13.80	13.80
Haden§	52	15.65	15.56

* The total circulating hemoglobin is determined by the formula: 13.8 gm. (Haldane normal standard) hemoglobin times percentage hemoglobin times total blood volume.

[1*]Males and females.

†According to the dye method.

‡Calculated on an erythrocyte count of 5,000,000.

§ Total volume value as high as 105 cc for each kg. have been found in three "normals." This group needs further study.

In Case XVII, oligocythemic hypervolemia was present in the first determination during the improvement period. The second determination was made sixteen months later while the patient was in relatively good clinical condition. During this interval with constant weight the total blood volume decrease was 1300 cc (20 per cent), 430 cc in plasma volume and 850 cc in cell volume. In spite of loss in cell volume, the percentage cells by hematocrit and the percentage hemoglobin had increased.

In Cases V and VI, the ratio of blood volume to body weight showed low normal values. In Case VI, with the patient recovering from shock, the hemoglobin decreased from 154 to 112 per cent within a period of six days. Unfortunately, volume determinations could not be made during the shock period. Six days later, the ratio of total blood volume to body weight was within the normal range. At this time the clinical condition was considerably improved. We believe that volume values would have been low in the acute period of suprarenal insufficiency. In Case XV, in which determinations were made within a period of eight weeks with no change in the clinical condition, practically identical volume values were found. The ratio of plasma volume to body weight was normal except in Cases IV and XVII, in which there were slightly increased values in plasma volume.

Concentration Data. The percentage blood water was increased in Cases I and V in which slight or moderate grades of anemia existed. In Cases XV and XVII, no definite anemia was present but the percentage blood water was somewhat high. In Case VI, a markedly low percentage of blood water was found. The first estimation was made while the patient was in profound shock with excessive vomiting and sweating, and with a systolic blood-pressure of 60. The hemoglobin and percentage of blood water revealed a state of marked dehydration. Six days later considerable clinical improvement had taken place. The hemoglobin had decreased 27 per cent. Definite dehydration still existed, as shown by the low percentage of cell and blood water. The percentage cell water was extremely low in the latter period (Table V).

The percentage plasma water was normal in all cases except Cases I, IV and V, in which mild hydremia was associated. In Case VI, during the shock period a low percentage of plasma water was present, which was restored to normal at the subsequent determination during the improvement period.

The percentage cell water showed considerable deviation from the accepted normal range (60 to 68 per cent). The water content of cells was abnormally high in Cases I, VII and XVII, while it was decreased in Cases III, IV and VI.

Discussion. As determined by our study, anemia is the exception rather than the rule in Addison's disease, having occurred in only slight degree in 37 per cent of the cases of this series. In only

TABLE V.—CONCENTRATION OF THE BLOOD AND PLASMA IN ADDISON'S DISEASE.

Case.	Date.	Whole blood, specific gravity.	Per cent.			Percentage, erythrocytes, hematocrit.	Percentage, hemoglobin, Palmer.	Remarks.
			Water content.	Plasma water content.	Erythrocytes water content.			
a								
1 (A 403755)	9–14–22	1.032	88.3	94.5	77.0	33	64	
	9–18–23	.....	85.7	94.0	....	..	72	
2 (A 401101)	9–14–22	1.047	82.5	92.5	66.0	43	105	
3 (A 407966)	11– 2–23	1.058	81.6	93.0	58.5	30	105	
4 (A 59466)	5– 3–23	1.052	82.6	92.6	67.0	39	114	
	8– 1–23	.....	79.7	93.4	58.0	38	103	
	2–26–24	.....	81.5	94.8	58.0	37	113	
5 (A 433553)	8–18–23	.....	85.2	93.6	62.0	27	82	
6 (A 291269)	7–13–23	.....	74.3	91.7	....	..	154	Patient in shock. Acute suprarenal insufficiency.
	7–19–23	.....	71.2	93.0	41.0	42	112	
7 (A 426922)	6– 7–23	1.057	80.0	92.4	73.0	41	119	
15 (A 458373)	3–24–23	.....	84.0	95.0	60.0	32	106	
	5– 9–24	.....	83.5	93.4	65.0	35	106	
17 (A 389986)	9–15–23	1.050	84.7	92.4	73.7	40	97	
	4– 3–24	.....	82.0	94.0	58.0	33	110	

one instance was marked anemia found. Since death followed within a very short period in 4 cases in which it was present, anemia may have a certain prognostic value in this disease. Repeated determinations of hemoglobin and cells reveal shifts which are explicable on the basis of volume fluctuations. The color index was 1 or less in every instance, averaging 0.9. The average hemoglobin by the Palmer method was 100 per cent in 12 cases, and by the Dare method 72 per cent for the entire series. The average cell-volume index was decreased and the average saturation index was normal in 5 cases, but Cases III and V showed indices greater than I. The average individual cell volume was decreased. The average percentage of hemoglobin in the individual cell was increased, especially in Cases III and V.

The leukocytic formulas revealed a relatively high incidence of lymphocytes, averaging 40.5 per cent. The total number of leukocytes for each cubic millimeter of blood showed no characteristic values, varying from normal to moderate leukocytosis.

The blood and plasma volumes were determined in a series of 9 cases. The average blood volume was 93 cc for each kilogram of body weight, and 3180 cc for each square meter of surface area. Normal volumes or normovolemias existed in every case except 1, in which a slightly increased total circulating volume with a decrease cell-plasma-volume ratio, oligocythemic hypervolemia, was found, which on later examination had returned to a normal relative value.

The plasma volumes in relation to body weight and surface area revealed normal values, averaging 54 cc of plasma for each kilogram of body weight, and 1890 cc for each square meter of surface area. The ratio of cell to plasma volume was decreased in 2 instances, Cases III and V having slightly decreased total blood volumes. In the other cases, the cell-plasma-volume ratios were normal. This is interesting in view of the anemia existing in Case I, as revealed by the percentage of hemoglobin and decreased percentage of cells by hematocrit, and indicates the relatively slight anemia. It was observed in Cases III, XV and XVII, with a definitely decreased percentage of cells by the hematocrit, that the percentage of hemoglobin was fairly normal. This would indicate that the erythrocytes were small, but had an increased content of hemoglobin.

Repeated determinations of blood and plasma volume were made in 2 cases. The time between determinations varied from three months to one year, and estimations were made in the periods of acute insufficiency and recovery. Marked shifts in plasma and cell volumes were found. Although determinations have been insufficient to warrant absolute statements, it seems probable that during the period of acute insufficiency lowered volumes exist which gradually increase during the recovery cycle. The volume changes, while definite, were not sufficient to disturb the normal relation of

volume to body weight.* The fluctuations include both cell and plasma volumes, revealing dilution and contraction processes associated with variations in circulating hemoglobin. In certain cases of Addison's disease under treatment, decompensation and compensation occur in stages. The former is associated with vomiting, diarrhea, sweating, and signs of excessive loss of fluids, resulting in a dehydrated state of the blood. In 1 case during the acute stage, the percentage hemoglobin reached 154, and dropped to 112 six days later when the condition had improved. Fluctuations in plasma volume probably take place in minor degree during the course of the disease. The changes in circulating hemoglobin could be interpreted as efforts to maintain the normal cell-plasma-volume ratios. These large volume shifts suggest those observed following diuresis in edematous states. The role of epinephrin in maintaining capillary permeability might be the factor explaining the volume changes.

The concentration values of the blood were definitely high in Case VI. This patient was extremely intolerant to epinephrin. With the administration of epinephrin, the systolic pressure dropped to a shock level. There was marked sweating, with vomiting and diarrhea, and during this period the hemoglobin was high. Following treatment to restore the fluids, such as application of heat, gradual improvement occurred. Six days later, repeated examinations revealed considerable improvement in the percentage of water in the blood and the hemoblobin had decreased markedly. This condition is extremely interesting, and possibly represents a sudden alteration in capillary permeability associated with the administration of epinephrin. Rowntree observed, in one instance, during the periods of acute epinephrin insufficiency, that small doses of epinephrin seemed to have no, or perhaps a deleterious effect, but when the full Muirhead treatment was used, there was a spectacular or marked beneficial response.

Summary. Of 17 cases of Addison's disease observed at the Mayo Clinic, definite anemia was present in only 1 (6 per cent). A mild or questionable anemia was found in 4 cases (23 per cent). In 3 of 5 cases the cell-volume index was decreased, and in three the saturation index was increased, indicating small erythrocytes with high hemoglobin content. A relatively high lymphocytosis was present in the majority of cases.

According to the dye method, normal circulating blood and plasma volumes, or simple normovolemias were found in all but 1 case. Decreased percentages of water and of blood and plasma were observed in 1 case during the period of acute suprarenal insufficiency. Anemia, when associated with Addison's disease, is apparently not due to a dilution, or an increase in total blood volume, since large blood volumes did not exist in the presence of anemia.

* Repeated blood and plasma-volume determinations by the dye method in normals have had a remarkable constant relation to body weight.

Anemia was not masked by contraction of volume, since normovolemia existed in all cases in which hemoglobin values were normal. Repeated volume determinations in 3 cases revealed in 2 marked fluctuation in cell and plasma volumes. The volume fluctuation masked only in a minor degree the percentage hemoglobin changes, since the normal cell-plasma-volume ratios were closely maintained.

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THE LEUKOCYTIC PICTURE IN CATARRHAL JAUNDICE (CHOLANGITIS).

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The wide divergence of opinion concerning the actual clinical picture and the underlying pathology of acute catarrhal cholangitis

doubtless explains the lack of unanimity with regard to its blood-picture. The extension of a catarrhal inflammation from the duodenum into the larger bile passages or an obstruction of these ducts by plugs of mucus are the commonly accepted explanations for this condition. However, the existence of an involvement of the finer bile radicals seems highly probable in view of the clinical course of certain cases of catarrhal jaundice, and, too, this process has been definitely proven in other cases coming to necropsy.[1]

Until the comprehensive studies of Jones and Minot,[2] no serious effort to establish a clinical entity in relation to acute catarrhal jaundice had been attempted. The characteristic clinical picture in the type of jaundice under discussion in this presentation commonly succeeds an acute upper respiratory infection by from five to fourteen days. Prodromal symptoms of lassitude, anorexia and headache are experienced for several days before the febrile manifestations of the disorder. The onset of the febrile reaction is accompanied, as a rule, by rigor, nausea and vomiting with or without upper abdominal distress or acute epigastric pain. Constipation with the classical clay-colored stool is the rule. At times diarrhea may attend the early stages of this affection. Extreme discomfort, restlessness, in part from the severe headache, and general malaise are remarked in the early febrile period. The temperature may range from 100° to 104° F. for three to five days before the appearance of skin pigmentation. Itching about the eyes may precede the visible jaundice which is first remarked in the scleræ and the soft palate. The general cutaneous surface quickly becomes tinged to a greater or less extent and all secretions, such as urine, smegma, and so forth, are likewise stained with bile pigments. Itching may become intense. Bradycardia is practically a constant finding. An enlarged somewhat sensitive liver may be determined very early in the febrile period. A majority of these cases show moderate splenic enlargement.[3]

The uncomplicated case of acute catarrhal jaundice responds promptly to simple dietetic and medical treatment. In mild cases the temperature falls to normal within three or four days; the subjective symptoms of gastric distress, nausea and vomiting usually subside with the fever; bile reappears in the stool in from six to ten days and the icterus simultaneously begins to fade. The complete disappearance of bile pigments from the urine usually antedates the loss of skin pigmentation by days or even weeks. Physical and mental depression are experienced for a considerable but variable period after the subsidence of acute symptoms.

Since the leukocytic reaction forms an important element in the composite picture of any infectious disease, it is interesting to examine the standard authorities with reference to this factor in catarrhal jaundice. No especial mention of this matter is found in the systems of medicine with the exception of Tice,[4] who states that

there is seldom an increase in the white blood corpuscles, though they may go up to 10,000. Von Limbeck[6] remarks no leukocytosis in simple, uncomplicated catarrhal jaundice. Cabot[6] states that a constant leukocytosis excludes uncomplicated catarrhal jaundice and points to malignancy or inflammation. Eighteen isolated numerical white cell counts are given, ranging from 4000 to 10,500. In this group ten counts are below 7500. Da Costa[7] quotes figures for the white cell count of catarrhal jaundice varying from 3600 to 26,000 with an average of 9361 in 40 cases. His cases without reference to the stage of the disease or the nature of the case are grouped thus:

Leucocytes.	Number of cases.
20,000 to 30,000	4
15,000 to 20,000	0
10,000 to 15,000	4
5,000 to 10,000	29
Below 5000	3

Emerson[8] lists 27 cases, in 20 of which the leukocytes numbered 10,000 or less; 3, 10,200 to 10,500 and 4 between 14,200 and 19,500. He remarked a rapid fall to normal after admission to hospital and quotes Bezançon and Labbé to the effect that a leukopenia follows in some cases.

A paucity of data on the numerical white cell count and an absence of a differential picture for catarrhal jaundice, therefore, existed until the above cited work of Jones and Minot.[2] The results of their extensive observations in this direction may be summarized as follows:

The white cell count is early increased, but rarely exceeds 10,000. This increase lasts but a few days and is succeeded by a leukopenia The lowest recorded count was 2000 and occurred in a very severe case. The leukocytes commonly fall below 4000 and the lowest level occurs a few days after the beginning subsidence of the jaundice. Return to normal is gradual, occupying a period varying from days to weeks. Leukocytosis is remarked only in complications.

The differential picture shows an early normal distribution or slight increase in the polymorphonuclear neutrophiles succeeded by a sharp drop in these cells (lowest 31 per cent in 5200) coincident with the fall in total leukocytes. There is an accompanying rise (relative and absolute) in lymphocytes and large mononuclears. With certain variations, these types assume their highest level at the height of the jaundice. Fifty to 60 per cent were high points for the lymphocytes, while the large mononuclears frequently reach 10 per cent. Eosinophiles and basophiles are usually within normal range. The eosinophiles, however, occasionally exceed 5 per cent of the total white cells. Especial attention is directed to the immaturity of the lymphocytes and the neutrophiles and to the appearance of vacuolization in the several forms of white cells.

The present study was begun two years ago and includes a series of white counts, total and differential, on 38 cases of acute catarrhal jaundice occurring among students in the University of Wisconsin. All blood was taken at 9 A.M., and differential leukocytic counts were made on 500 cells as a rule. Bunting's figures[9] for the normal numerical and differential leukcoytic counts have served as a basis for comparison:

	Limits. 6000–8000	Average. 7500
Neutrophiles	50.0–60.0	54.0 (3780)
Eosinophiles	0.8– 4.0	3.2 (240)
Basophiles	0.4– 1.8	0.8 (60)
Small and large lymphocytes	30.0–40.0	33.0 (2475)
Large mononuclears	0.6– 2.0	1.6 (120)
Transitionals	6.0– 8.0	7.4 (555)

Bunting, in a later publication,[10] qualifies these figures by a statement that they may depend in a measure on the prevalence of "low grade chronic non-disabling infections, particularly of the upper respiratory tract which are particularly prevalent in the locality in which my counts were made." This statement does not invalidate the use of his leukocytic formula as the norm for the community in which these studies were made.

In the appended table (pp. 62–63) under the separate days preceding and succeeding the onset of the jaundice have been tabulated the blood-pictures of the several cases. The wide fluctuations and paucity of figures in the individual groups do not admit of striking accurate averages.

LEUKOCYTIC PICTURE IN CATARRHAL JAUNDICE.

BEFORE ONSET OF JAUNDICE.

Case No.	White blood cells.	Neutrophiles.		Eosinophiles.		Basophiles.		Lymphocytes.				Lymphoblasts.		Large mononuclears.		Transitionals.	
								Small.		Large.							
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
								FOUR DAYS.									
24	7,400																
34	3,800	78.8	2994	1.4	53	0.4	15	12.2	464	2.8	106	..	..	4.2	160		
								THREE DAYS.									
24	3,100	35.5	1100	1.5	47	..	..	Tot.	55%	1705	..	..	..	1.5	47	6.5	201
34	6,000	70.4	4224	3.8	228	0.6	36	14.2	852	7.0	420	1.2	72	2.8	168		
								TWO DAYS.									
6	12,800	68.6	8781	5.8	742	..	..	19.2	2458	5.8	742	0.2	26	..	..	0.4	51
27	5,000																
32	8,200	62.0	5084	..	..	..	..	Tot.	33%	2706	..	1.0	82	2.0	164	2.0	164
34	5,200	41.2	2142	3.6	187	0.6	31	39.2	2038	11.0	572	4.0	208	0.4	21		
								ONE DAY.									
5	5,800																
32	5,200	62.0	3224	4.0	208	..	..	Tot.	27%	1404	..	..	..	1.0	52	6.0	312
43	6,000																

LEUKOCYTIC PICTURE IN CATARRHAL JAUNDICE.—(*Continued.*)

AFTER ONSET OF JAUNDICE.

Case No.	White blood cells.	Neutrophiles.		Eosinophiles.		Basophiles.		Lymphocytes.				Lymphoblasts.		Large mononuclears.		Transitionals.	
								Small.		Large.							
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
								DAY OF ONSET.									
1*	14,000																
7	8,000																
12	6,600	61.0	4026	3.0	198	2.0	132	Tot.	30%	1980	..	..	..	..	..	4.0	264
20†	17,200																
23	6,800	66.0	4488	2.0	136	..	..	Tot.	27%	1836	..	..	..	..	..	5.0	340
26	2,800	57.5	1610	2.0	56	..	..	Tot.	28.5	798	..	..	..	8.0	224	4.0	112
27	6,200																
28	5,000	58.0	2900	0.5	25	1.0	50	Tot.	28.5	1425	..	..	..	0.5	25	11.5	575
29	7,400	57.5	4255	0.5	37	1.0	74	Tot.	36%	2664	..	..	..	3.5	259	1.5	111
33	10,000	67.4	6740	0.4	40	0.2	20	23.4	2340	8.0	800						
35	3,200	50.2	1606	1.0	32	0.2	6	35.6	1139	12.4	397	0.2	6	0.4	13		
36	2,400	60.0	1440	3.2	77	0.8	19	20.0	480	5.2	125	0.8	19	9.8	235	0.2	5
37	4,800																
43	4,400																
Average.	7,570																
								ONE DAY.									
2	4,600																
3	6,800																
4	5,200																
10	11,000																
14	5,000																
19	5,200	64.0	3328	3.0	156	..	..	Tot.	29%	1508	..	..	..	1.0	52	3.0	156
22	8,400																
25	4,800																
26	4,600	62.0	2852	1.0	46	0.5	23	Tot.	26.5	1219	..	..	..	8.0	368	2.0	92
27	2,800	29.5	826	0.5	14	0.5	14	Tot.	58%	1624	..	..	..	8.5	238	2.0	56
36	5,800	54.2	3144	1.8	104	1.2	70	21.0	1218	5.6	325	0.4	23	15.8	896		
38	4,000																
41	7,200	66.6	4795	0.8	58	..	..	16.2	1166	16.0	1152	0.4	29				
43	4,200	50.2	2108	2.4	101	0.8	34	38.2	1604	8.0	336	..	..	0.2	84		
Average.	5,685																
								TWO DAYS.									
7	8,600																
9	5,400																
11	7,000																
16	8,600	47.0	4042	2.0	172	..	..	Tot.	45%	3870	..	..	..	3.5	301	2.5	215
17	7,200	58.0	4176	6.0	432	..	..	Tot.	30%	2160	..	..	..	..	..	6.0	432
18	8,000																
25	4,200	53.0	2226	4.0	168	..	..	Tot.	38%	1596	..	..	..	..	..	4.0	168
27	5,200																
35	4,400	42.8	1883	3.4	150	0.6	26	34.4	1514	16.8	739	..	..	2.0	88		
36	2,400	60.0	1440	3.2	77	0.8	19	20.0	480	5.2	125	0.8	19	9.8	235	0.2	5
37	2,800	45.6	1277	1.8	50	0.4	11	37.6	1053	12.8	358	0.8	22	1.0	28		
Average.	5,800																
								THREE DAYS.									
36	6,000	63.8	3828	1.4	84	0.2	12	15.8	948	3.4	204	1.4	84	14.0	840		
38	4,600	45.6	2098	1.6	74	0.4	18	43.0	1978	8.8	405	0.6	28				
44	1,200	46.6	559	1.0	12	0.2	2	32.8	394	16.8	202	1.0	12	1.6	19		
								FOUR DAYS.									
36	4,800	48.0	2304	3.0	144	0.5	24	29.0	1392	6.0	288	..	..	13.0	624		
42	8,600																
37	5,200	51.8	2694	1.8	94	0.8	42	31.0	1612	10.6	551	0.8	42	3.2	166		
								FIVE DAYS.									
36	3,600	53.0	1908	2.0	72	0.8	29	26.6	958	7.6	274	0.4	14	9.6	346		
37	6,400	45.4	2906	2.6	166	0.4	26	37.8	2419	11.4	730	1.0	64	1.2	77	0.2	13
								SIX DAYS.									
15	6,000																
36	2,800	55.2	1546	3.6	101	1.0	28	23.2	650	6.8	190	0.2	6	9.8	274	0.2	6
42	4,400	44.0	1936	3.8	167	0.4	18	42.8	1883	7.0	308	..	..	1.4	62	0.6	26
								SEVEN DAYS.									
36	4,400	40.8	1795	4.0	176	0.8	35	42.4	1848	6.4	282	0.2	9	5.8	255		
37	4,000	53.0	2120	2.2	88	1.2	48	30.0	1200	11.8	472	0.6	24	1.0	40	0.2	8
								EIGHT DAYS.									
16	8,800	59.0	5192	1.0	88	1.0	88	Tot.	36%	3168	..	..	..	1.5	132	1.5	132
36	3,200	47.6	1523	4.0	128	0.4	13	30.0	960	6.4	205	0.4	13	10.8	346	0.4	13
44	3,800	45.8	1740	1.0	38	0.8	30	41.2	1566	8.0	304	1.2	46	2.0	76		
								NINE DAYS.									
30	9,000																
36	4,400	42.8	1883	4.2	185	0.8	35	32.2	1417	9.8	431	2.0	9	9.6	422	0.4	18
44	3,200	58.0	1856	1.8	58	..	..	31.0	992	6.8	218	0.4	13	1.8	58	0.2	6

* Case 1. Diarrhea for two days. † Case 20. Vomiting copiously for two days.

Excluding Cases 1 and 20, average total leukocytic count for the remaining 12 cases on the day of onset of jaundice was 5633.

In Chart I the numerical leukocytic counts have been plotted to demonstrate better the distribution of these figures. It immediately becomes apparent that only a small minority of the counts

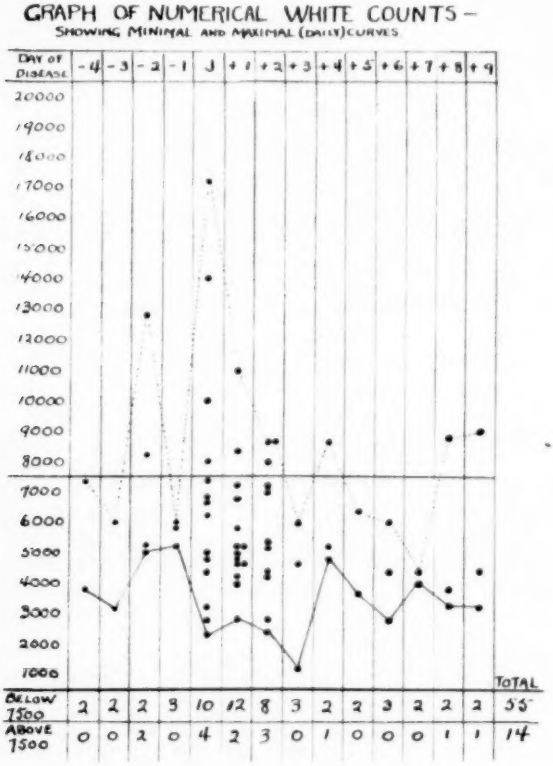


CHART I.

(14 of 69—20.2 per cent) exceed the average normal level. A further analysis of the total leukocytic counts in the 38 cases under study shows at the highest recorded level for each individual case the following:

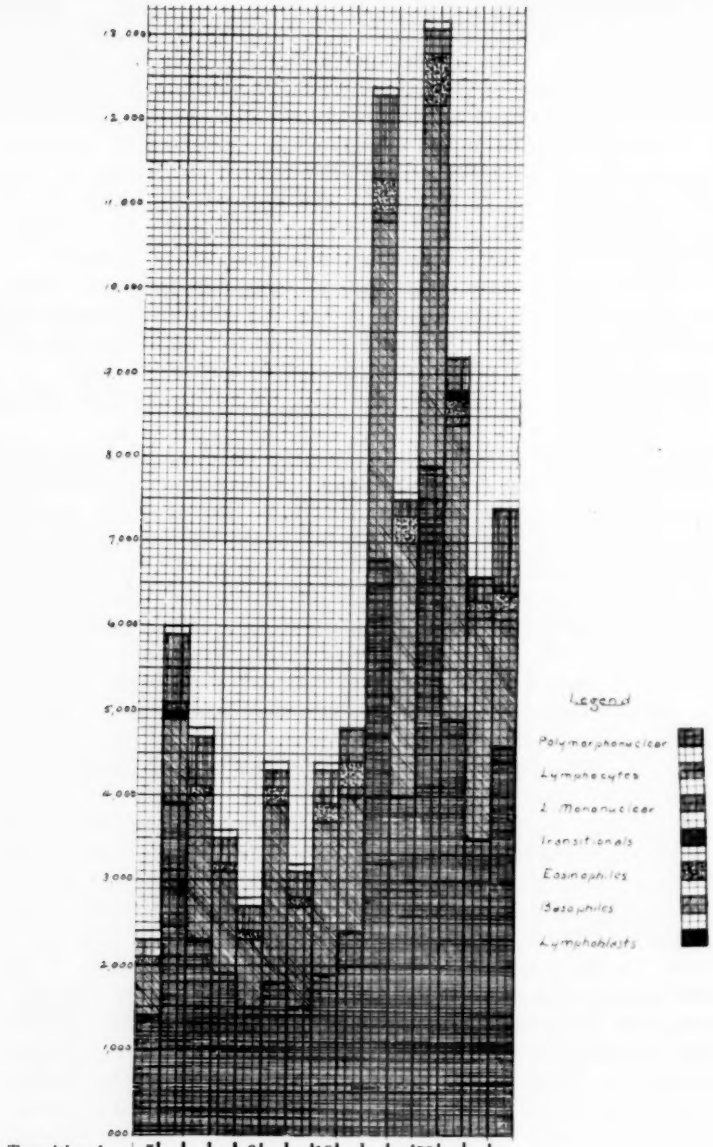
Leukocytes.	Cases.
Over 15,000	1
10,000 to 15,000	4
7,500 to 10,000	9
5,000 to 7,500	17
2,500 to 5,000	7

The tendency to leukopenia is quite definite and, contrary to the contention of Jones and Minot, is an early finding in catarrhal jaundice. Indeed, a majority of the studied cases showed a definite leukopenia not only at the very onset of the manifest jaundice but

several days before its appearance. With the development of jaundice the reduction of the white corpuscles becomes pronounced. The lowest count, 1200, (Case 44) was recorded three days after the onset of jaundice. The period of leukocytic depression is variable and apparently in a measure dependent upon the severity of the underlying condition. A return to the normal leukocytic level occupies from ten to fourteen days in the average case, and is commonly preceded by a postfebrile reactive leukocytosis (Chart II).

The differential leukocytic picture of catarrhal jaundice offers certain difficulties of translation unless the absolute counts be given due consideration. Confusion is bound to result from discussion of the relative or percentage changes in the various cells. A characteristic case has been charted with an analysis of the component cells (Chart II).

Beginning with the second day after the onset of jaundice this case has been followed for fifteen days. A depression of polymorphonuclear neutrophiles (normal, 3780) is immediately noted, which continues for ten days. This fall in the neutrophilic count is relatively constant (see Table), notable examples being Case 27 on the first day after the onset of the jaundice and Case 44, three days after the onset. In the former the neutrophiles numbered only 826 (29.5 per cent of 2800), whereas a figure of 559 (46.6 per cent of 1200) was established for these cells in the latter. High relative lymphocytic counts may lead to an erroneous conception of a replacement of the neutrophiles by these cells. However, it becomes apparent that this discrepancy results not from an actual increase in the lymphocytes (normal, 2475) but from a disproportionate reduction in the neutrophiles (Table and Chart II). Indeed an absolute lymphocytosis is most unusual in spite of occasional relative changes as high as 58 per cent with the polymophonuclear neutrophiles at 29.5 per cent in a total white cell count of 2800 (Case 27, one day after the onset of jaundice). In Chart II the lymphocytes resume their normal absolute level simultaneously with the neutrophiles in spite of relative preponderance over the latter at several points in the earlier days of the disease. Unusual young forms of lymphocytes and the common appearance of lymphoblasts bespeak a definite stimulation of the lymphoid centers. Furthermore, there is, commonly, an absolute increase in the large mononuclear cells (normal, 120), the highest level being recorded in Case 36 on the first day after the onset of the jaundice (15.8 per cent of 5800 — 896). The transitional cells are practically always below the normal absolute level (555). The eosinophiles (normal, 240) and basophiles (normal, 60) partake of the general decrease in polymorphonuclear forms with certain well-defined exceptions in the case of the first named. In Case 6 on the second day prior to jaundice (5.8 per cent of 12,800 — 742) and in Case 17 two days after the onset of jaundice (6 per cent of



Transitional		5				6				18					53					
Basophile		19	12	24	29	28	35	13	35				61	26						
Lymphoblast		19		24	14	5	9	12	9		25	15								
Date	Month	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Day	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21				
	Year	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24				

Normal (Bunting)

CHART II

7200 — 432), increases in both the relative and absolute figures for the eosinophiles were determined.

Discussion. The leukocytic picture in a series of 38 cases of catarrhal cholangitis is presented. Notable among the findings in this relation are the leukopenia, the absolute decrease in all of the component white blood corpuscles except the large mononuclear cells and the appearance of unusual lymphocytic forms, especially the lymphoblast. Preliminary studies indicate that the fall in polymorphonuclear neutrophiles results from inhibition rather than paralysis of the leukogenetic function. The suggestion of a continued hemoclastic shock in explanation of the observed leukopenia in the presence of a known hepatic lesion has not been fruitful.

Summary. 1. Leukopenia is an almost constant blood finding in uncomplicated catarrhal cholangitis. In a certain percentage of cases it may precede the appearance of the jaundice. In cases followed long enough a definite postfebrile, reactive leukocytosis is remarked.

2. The polymorphonuclear neutrophiles suffer more than any other white-blood element in the primary depression.

3. This disproportionate decrease of the neutrophiles leads to a relative lymphocytosis, but the actual number of these elements is decreased as a rule.*

4. The large mononuclear cells alone appear to be constantly increased in catarrhal jaundice.

5. In moderate cases a return to the normal numerical and differential counts occurs within two weeks.

From a practical standpoint these data should serve as important diagnostic criteria. Prognosis in catarrhal jaundice may be guided by the degree of the leukopenia and the trend of the leukocytic curve. As has been intimated, the degree of leukocytic depression is frequently in direct ratio to the severity of the underlying condition. Furthermore, the lowering of resistance incident to a decrease in the leukocytes in catarrhal cholangitis must impress the practitioner with the necessity for the protection of such individuals from exposure to infectious disease, until a normal leukocytic level has been reëstablished.

* Jones and Minot's conclusions of an early primary leukocytosis, transient in nature and minor in degree, and of an almost constant absolute lymphocytosis "in spite of the leukopenia" which supervenes, are in disagreement with these findings. In justice to these workers it should be stated that a critical review of their data shows a leukopenia in a majority of cases from the onset and, too, the instances of absolute lymphocytosis are the exception rather than the rule. Such instances apparently occur more commonly than have been remarked in the present study but far less frequently than the conclusions of Jones and Minot would infer. In a word a definite but inconstant tendency in this direction is noted throughout the course of a small minority of their cases, and more especially in the presence of a leukocytosis.

If these two points of difference be reconciled, it will become apparent that the present studies closely corroborate the work of Jones and Minot.

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THE INFLUENCE OF EMOTIONAL REACTIONS ON BASAL METABOLISM.*

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This study was prompted by the observation that basal metabolism readings of psychoneurotic individuals without goiter, no matter how careful the technic, are sometimes high.[1] In an attempt to learn something of this problem methods were used to determine the effect of emotions on basal metabolism. Patients were selected who were known to have aspects to their past history which were emotion producing. None of them had a goiter.

A patient was placed on the bed after the usual preliminary preparation for a basal metabolic rate which was determined by the Tissot-Haldane method. Other points in the technic were carried out as described by one of us.[2] Three basal metabolic tests were made which were identical except that during the second the patient was asked to keep quiet as before, but to think about something (the thing was suggested to the patient) which from his history would seem to induce emotions. The patient was under careful observation all of the time during the second test, for objective signs of emotional responses. Notes were taken. Before each test the patient was urged to be as quiet as possible. After all of the tests had been made the patient was interviewed to ascertain what his subjective feelings had been. It will be observed that by this procedure the test in which the patient was expected

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to have emotional responses was sandwiched, so to speak, between two control tests.

Two case histories, at this point, with the actual data of the tests, will serve to show more exactly the procedure of the study.

Case Reports. CASE I.—C. B. F., aged thirty-four years, single, farmer, college graduate, complained of being torn up by the slightest excitement; he said his heart would beat rapidly and he would become short of breath, and had difficulty in talking at these times. He comes of a family in which a paternal uncle developed mental changes after an injury to the head; another paternal uncle lived a hermit's life after domestic trouble; a maternal uncle was insane; a maternal aunt was nervous; and one sister of the patient developed a kind of paralysis of the legs and was in bed weeks following a minor excitement, from which she recovered. The patient had always been reserved and retiring and was occasionally depressed. His early life was uneventful from the standpoint of disease or circumstance until he had reached high school when he was troubled with his eyes, was restless, and had a slight speech defect. He slept poorly and said he always had a feeling that something was going to happen. He was fitted with glasses and the symptoms were less bothersome. In college the speech defect returned but he struggled with his "weakness" by taking a course in public speaking. He had a good occupational record.

In 1918, the patient was drafted into the United States army and soon became markedly upset by the restrictions and discipline of the army. On the way overseas he met with some unpleasant experiences in the influenza epidemic, and contracted the disease himself, from which he recovered slowly because of insomnia, weakness and rapid heart. Thereafter, he had some difficulty in speaking to some officers who were rather rough to him, and a marked degree of "self consciousness" with a violent distaste for army life developed, which upon his return home caused him to seclude himself assiduously.

The only positive physical findings on admission to the hospital were some mild dental caries, blood-pressure 102–70, and bilateral pes planus.

From the behavioristic standpoint he showed a tendency to be alone and become agitated and markedly restless. Whenever army life, and his own army experience in particular, was mentioned, he showed much disgust.

The data of the test are given in Protocol I.

PROTOCOL I. *C. B. F.*—Anxiety Hysteria. September 5, 1922, 9.30 to 10.30 A.M.

Stimulus Remarks for Test B. Remain quiet as before and think over in the next ten minutes your army experiences, especially the more disagreeable ones.

Objective Observations during Test B:

10.00½ Test began (stopcock opened). (Began to detail stimulus remarks).
10.03 Face flushed; quiet; eyes closed.
10.04 Breathing becomes heavier; quiet.
10.04½ Takes occasional larger breath; quiet.
10.05 Breathing irregular in rhythm; otherwise quiet.
10.07 Slight fine tremor in respiratory movements as if large movements would break up into many smaller ones.
10.08½ Whole upper half of body shows definite fine tremors; face slightly flushed.
10.09 Fine tremors of upper half of body continue. Presents slight facial contortions or grimaces; eyes shut; face flushed.
10.10 Fine tremors, more marked in upper half of body; smiles; face continues flushed.
10.10½ Stopcock closed.

Subjective Reactions during Test B. Felt confined by the local discomfort of having nose pinched. Did not think he would get worked up like he did. Was disgusted and somewhat angered to think he would react as much as he did. Said he had a real emotional disturbance in which he could feel his heart beat more rapidly, with a dull sensation in the region of the heart.

Metabolic Readings:

B. M. R. (first control) A	B. M. R. (emotional response) B	B. M. R. (second control) C
+9.62	+28.9	+13.9

CASE II.—S. J., aged thirty-two years, married, bookkeeper, complained of headaches with pain in back of head on stooping, restlessness, insomnia, fear of insanity, and with an impulse to scream when in public places. He comes of a family free from nervous and mental diseases. Aside from being a quiet and uncommunicative youth, there was nothing unusual in his early history. He was an average student in school, having reached the seventh grade when he quit to go to work. He worked quite regularly until enlisting in 1917. Soon thereafter he was detailed to be a male nurse in the Medical Department in a camp in the United States. Once was ill after being struck by an automobile, after which his headaches and dizziness began. Soon thereafter, while on night duty, he was accused of being asleep, was severely reprimanded, reduced in rank, and placed in the guardhouse for thirty days. Certain other grave punishments were held before him as possibilities. He was very much worried by the affair and felt differently thereafter.

Physical findings revealed a few dry rales over the right apex

posteriorly, clubbing of all fingers and toes, fine tremors of extended fingers, bilateral hyperopia, and dental caries and gingivitis.

He showed on admission to the hospital considerable anxiety and restlessness, especially when talking over the painful incidents of his army life, and on a few occasions tears came into his eyes. He was somewhat suspicious, but had no definite delusions, ideas of influence, ideas of reference, or hallucinations. Protocol II gives the data of the laboratory tests and observations.

PROTOCOL II. S. J. Anxiety Neurosis. September 21, 1922. 9.00 to 10.00 A. M.

Stimulus Remarks for Test B. Be quiet as before and in the next ten minutes think over your army experiences, especially the unpleasant ones.

9.39 Stopcock opened. (Began to detail stimulus remarks.)
9.40 Quiet; normal.
9.41 Face pinker.
9.42 Face pink. Breathing increased in amplitude and rate. Bats eyes frequently.
9.43 Breathing heavily.
9.44 Heavy breathing.
9.45 Slight tremor of upper extremities; tears appear at eyes and run down over cheek; face red; apparent suppressed crying.
9.46 Breathing irregular.

Subjective Reactions. Patient stated that the remarks made him markedly blue and depressed for the time being. Said his emotions were intense and were most intense about the middle of the test.

Metabolic Readings:

B. M. R. (first control) A	B. M. R. (emotional response) B	B. M. R. (second control) C
−2.8	+40.0	+.8

It has been known that emotions affect the metabolism readings and are to be avoided, where possible, in arriving at conclusions for diagnostic purposes. In this study the variations in heat production induced by thinking of certain things, usually of an undesirable nature, were interesting for several reasons. Table I gives the data for 14 psychiatric patients with various diagnoses. One patient was given the test twice.

To the casual observer the majority of these patients would have been considered during the test as lying still on the bed. It was recorded in the case of 4 that there was restlessness, which was small in 3 cases. The most constant objective reactions observed were small changes in amplitude and rate of respiration, very fine tremors, and changes in the color of the face from normal to a flushed face, as in blushing, with irregular variations throughout the second test.

TABLE I.

Diagnosis.	Metabolism.			Feelings during test B, subjective.	Detailed objective observation during test B.	Summary of objective observations.
	A.	B.	C.			
S. J. (anxiety neurosis)	−2.8	+40.0	+0.8	Depressed	Flushing of face; change in respiratory rate and amplitude; few tremors in upper part of body; tears in eyes	Very slight reaction.
C. B. F. (anxiety hysteria)	+9.6	+28.9	+13.9	Disgust; anger	Flushed face; change in respiratory rate and amplitude; fine tremors in upper part of body	Very slight reaction.
J. H. (anxiety hysteria)	+7.0	−8.0	+3.5	Slightly depressed	Flushed face, change in breathing amplitude and rate; breathing with lungs full; occasional small twitch	Nothing unusual.
J. H. (retest with new stimulus remarks)	−1.3	−5.6	−3.5	"Peeved;" more feeling than on previous test.	Same as above; no tremors; alert	Nothing unusual.
C. E. R.* (anxiety hysteria)	+12.4	+14.0	+4.3	Excited feeling	Coughed few times, restless, occasionally moving arm or leg or head about slightly	Slightly restless.
P. O. C. (anxiety hysteria)	+7.8	+23.0	+4.6	No emotional reactions	Flushed face; possibly some change in breathing amplitude	Nothing unusual.
B. L.† (anxiety hysteria)	−2.5	+17.2	+14.9	Tense and excited	Slight tremors of neck and shoulders; face not changed	Very slight reaction.
S. E. (hysteria)	+11.4	+31.9	+13.2	No emotions; local nasal discomfort	Restless, moves legs, arms, and head about; small tremors about face and neck; breathes irregularly	Slightly restless.
S. H.‡ (hysteria)	+5.5	+21.0	+13.1	Excited	Face pink to red; tremors of face and neck; tremors increased to end of test; breathing irregular	Restless.
S. R. (hysteria)	+5.8	+13.9	+12.2	Slightly depressed	Changes in color of face; possibly amplitude of breathing slightly increased	Nothing unusual.
Y. H.§ (neurasthenic type)	+0.2	+8.6	−5.6	None	Face pink; slightest restlessness for short time	Nothing unusual.
S. W. (neurasthenic type)	−1.1	+22.0	+8.7	None	Face pink; probable slight increase in amplitude of respiration	Nothing unusual.
S. B. F.** (neurasthenic type)	+8.8	+24.6	+9.2	Excitement in which heart felt accelerated and breathing came harder	Face pinker at times	Nothing unusual.
R. C. J. (constitutional psychopathy with depressive and anxiety features	+3.0	+15.2	+8.6	Slightly excited	Slight tremor of upper part of body; shallow, frequent respirations; some squirming	Very slight reaction.
L. N. (constitutional psychopathy with schizophrenic features	+20.5	−1.3	+50.9	Revulsive feelings	Grimaces of face; respiration deep and slow; eyes opened and closed; face pink; tried to speak a few words	Restless.

* Felt more fatigued than usual at the end of the day on which test was made.

† The test initiated an excitement which he could feel all day.

‡ Reacted by marked tics and muscle spasms for twelve hours after the test.

§ More study of Y. H. revealed fact that stimulus remarks used were not "his chief preoccupation."

** Said he was always so fatigued that emotions were short-lived.

NOTE.—There seems to be little correlation between the change in metabolism and the objective manifestations of emotions.

Subjectively, the reactions varied; 3 said they felt depressed; 1 reacted by a combination of anger and disgust; 1 reacted by being "peeved" and 1 by revulsive feelings; 5 said they were more or less excited; 4 had no feelings whatsoever. On J. H. two tests were performed with different stimulus remarks and the emotional responses differed with a reduction in the metabolic rate in either test.

Chart I presents in graphic form the metabolism readings for the group and shows rather strikingly the tendency for the rates to increase in the majority of cases. There are indications, however, that emotions affect metabolism in opposite ways and this suggests the possibility of two distinct types of people.

The preliminary nature of this study is evident from the few cases studied but nevertheless Table I presents some interesting facts corroborated by clinical observation. One of the most striking facts is the failure of some patients to recognize any emotion though readings clearly indicated a rise of metabolism. This offers one hopeful explanation for the insidious way in which neurasthenic individuals may dissipate their energy. Another important fact is the change in metabolism in a few cases without objective evidences except small vasomotor phenomena, very fine tremors, and slight changes in respiratory rate and amplitude. These give clues for the detailed study of the elusive emotional states. Two patients, P. O. C. and S. W., had no subjective feelings and very slight objective behavior changes. Except for the change in metabolism, practically nothing would have been known of the de-energizing tendency of the stimulus remarks about which these patients were preoccupied almost continually. By comparative studies[3] it was shown that some of the patients' emotional reactions, in terms of energy expended, were equivalent to that of an ordinary hospital ward patient, or from one-third to one-half of the energy necessary for the same patient to do the work of a merchant tailor.

No characteristics peculiar to the different neurotic types was ascertainable with such a small number. The study bears out what most clinicians have long observed, viz., that the mere fact of a patient lying quietly in bed, is no assurance of a state of rest. The pharmacodynamic importance of certain ideas and imaginations, obsessive thoughts, painful reminiscences and complex material, is at once apparent. It must be evident that unless something is known about the life problems of a patient and their effect on him, mistakes of diagnosis may easily follow from too much dependence on basal metabolic determinations. This is all the more true in a region such as the Great Lakes district where a rather high per cent of all people have goiter. The energy governing mechanism of subtle emotional reactions should stimulate study of such a disease entity as exophthalmic goiter, the etiology of which seems definitely disputed, to determine what components of it may be

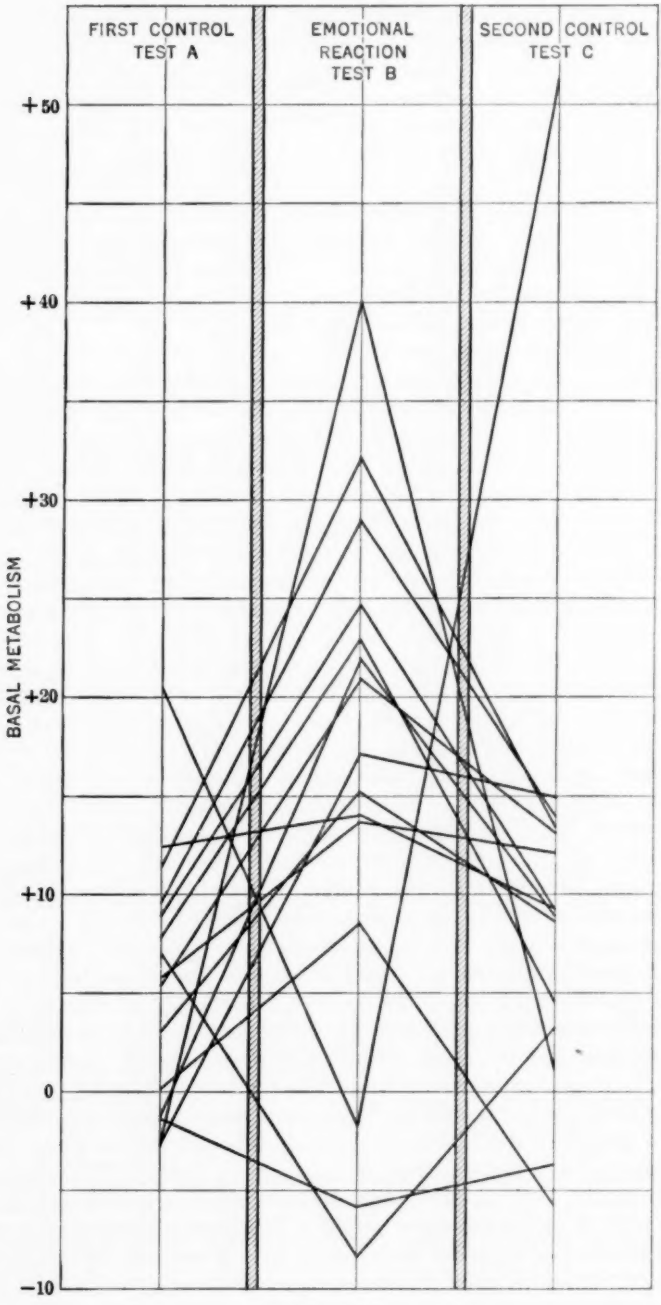
FIRST CONTROL
TEST A
EMOTIONAL
REACTION
TEST B
SECOND CONTROL
TEST C
+50
+40
+30
+20
+10
0
−10
BASAL METABOLISM

CHART I.

actually due to the secretion of the thyroid and what may be due to a lowered threshold for emotional reactivity.

Summary. 1. Basal metabolism above normal in some psychoneurotic individuals without goiter prompted an inquiry into the mechanism of the deviations.

2. Psychoneurotics without goiter usually respond when thinking about an emotion-producing aspect of their past history, by an increased metabolic rate.

3. Most frequent objective responses to emotion-producing stimuli were small changes in color of skin, slight change in rate and amplitude of respiration, and very fine tremors.

4. Some patients who showed increase in metabolism and practically no objective reactions, were not aware of any emotions whatsoever.

5. The pharmacodynamic influence of unpleasant memories, ideas, and worries is a subject worthy of much investigation in order to understand the phenomena of disease and discomfort, and the conservation of human energy.

6. Lying apparently still in bed is not to be taken as a criterion of rest.

7. Exophthalmic goiter with disputed etiology should be studied to see what components are due to secretion of thyroid and what may be due to lowered threshold of emotional reactivity.*

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* The writers are indebted to Surgeon Lawrence Kolb, of the United States Public Health Service, for his approval and encouragement of this study, and to the staff of the U. S. Veterans Hospital No. 37, Waukesha, Wisconsin for coöperation during the course of same.

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THE ELECTROCARDIOGRAM IN UREMIA AND SEVERE CHRONIC NEPHRITIS WITH NITROGEN RETENTION.

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A previous publication[1] from the Massachusetts General Hospital has called attention to the fact that disturbances of cardiac mechanism are not uncommon in uremia. We have made a more detailed study of 38 cases of uremia and severe chronic nephritis with nitrogen retention to determine whether abnormal electrocardiographic changes may be ascribed to the toxic effect of the products of uremia upon the heart muscle. The effects of digitalis, myxedema, myocardial degeneration and disease of the conduction system have been excluded so far as possible.

There is little in the literature on this subject. Lewis[2] has noted that many poisons may act upon the end-deflection of the electrocardiogram but that the initial phases are less liable to change of form and direction. Cohn[3] has described the effects of digitalis and atropin on the *T* wave. He also mentions the fact that muscarin will invert the *T* wave. Kraus and Nicolai[4] say that in poisoning there may be first an increase, then a decrease in the *T* wave. They also note that decrease or disappearance of the *T* wave may occur in loss of blood and in chloroform narcosis.

All of these writers refer to exogenous poisons. Among the toxins of endogenous origin which affect the heart that of thyroid disease is perhaps one of the commonest. The toxin of this disease however causes only changes of heart-rate at first and not until secondary heart muscle changes set in is the form or direction of the complexes

of the electrocardiogram notably changed. The toxins of various diseases will cause changes in rate but probably none of these with the exception of the toxin in diphtheria produces changes in the form of the electrocardiogram. We believe that a toxemia occurs in uremia which affects the heart muscle in certain instances so that a change in either the form or direction of the electrocardiographic complexes may occur. Heitz[5] recalls that in 24 of his 25 cases of pulsus alternans there was uremia. Chalier and Centaminin also found uremia in 7 of their 10 cases of pulsus alternans. Both hypertension and uremic poisoning were probably factors in these cases.

Thirty-eight cases of uremia and severe chronic nephritis with increased blood nitrogen have been studied at the Massachusetts General Hospital with reference to the electrocardiogram. All showed a non-protein nitrogen amounting to 69 mgm., or over, per 100 cc of blood. As already noted above, the effects of myxedema, digitalis, myocardial degeneration and disease of the conduction system have been excluded so far as possible.

Exclusive of these complicating factors there were 12 of the 38 cases with abnormal changes in the electrocardiogram (other than abnormal axis deviation, sinus arrhythmia or tachycardia) which could not be wholly accounted for except by the consideration of a toxic effect of the products of uremia upon the heart muscle. Of the 12 positive cases none had a history of rheumatic fever or chorea and none showed physical signs of valvular heart disease. All had negative Wassermann reactions except 1 (serial No. 35, Table 1) and there was no history or physical sign of lues in this patient, who was aged twenty years. The greatest age in the positive group was forty-three years and the lowest twenty years, with an average age of thirty and one-half years. This makes arteriosclerotic heart disease unlikely as a causative factor in the production of these abnormal electrocardiograms.

Nine of the 12 cases received no digitalis either as determined by history or while in the Massachusetts General Hospital. One case (Serial No. 26) received the equivalent of 0.8 gm. of the dried digitalis leaf over a period of ten days and another case (No. 32) received 0.3 gm. over a period of seven days. The digitalis effect in both these cases we believe was negligible. Cohn[3] found changes in the *T* wave in several cases after the equivalent of 0.6 to 0.8 gm. of the dried leaves of digitalis administered at the rate of 0.4 gm. daily, but the more usual amount found by him which was needed to produce changes in the *T* wave was 1.2 gm. in three days. A third case (No. 25) received the equivalent of 1.2 gm. of the dried leaves of digitalis in eleven days. This may have in part contributed to the change in form of the electrocardiogram but these changes were so marked that the record is included as undoubtedly the result in part at least of uremia.

TABLE OF 12 CASES OF UREMIA

Serial number.	Age.	Sex.	Edema.	Albuminuric retinitis.	Non-protein nitrogen.	Amount digitalis before Ecg.	Rhythm.	Auricular rate
13	42	M.	Feet and legs	+	Urea nitrogen 98 mg.	0	Normal	115
19	32	M.	Feet and legs	+	125	0	Normal	95
21	33	M.	Eyelids feet and legs	+	105	0	Normal	75
23	22	M.	0	+	83	0	Normal	98
25	43	M.	0	+	99 142 153	Total of 1.2 grams digitalis in 11 days	At first no evidence of auric. activity, auric. standstill and idioventricular rhythm. Later, probably auricular fibrillation and *A-V* rhythm. Still later (on day of death) a regular tachycardia, probably normal rhythm	
26	34	F.	Slight of feet	0	333	Total of 0.8 gram over a period of 10 days	Sino-auricular block with ventricular escape. Later varying from ectopic auricular rhythm to ventric. escape or to *A-V* rhythm	? 30 to 50 90 with ectopic auric. rhythm, otherwise 60
29	43	F.	0	0	201	0	Normal rhythm	80
30	35	F.	0	+	153 to 220	0	Sino-auricular tachycardia	115
31	22	M.	Marked general edema	0	69 38 one month later	0	*a*, Sino-auricular bradycardia ? *S-A* block. *b*, After 1 month with marked improvement. Normal rhythm	40 65
32	43	M.	Ankles and sacrum	Papilledema both discs. Some exudate. Not typical albuminuric retinitis	174	0.3 gram over a period of 1 week	Sino-auricular block variable in Lead II every 4th beat. One dropped beat from *A-V* block in Lead III	Varying, 70 to 90
35	20	M.	0	+	70 to 111	0	Normal	90–100
36	21	F.	0	Fundi not examined	82	0	Normal	110

Ventricular rate.	P-*R* interval.	Axis deviation.	P wave in Lead II.	Q–*R*–*S* complex.	*T* wave.
115	.16 sec.	Normal	P_2 notched, +1	Normal	T_1 − 1 mm. T_2 flat. T_3 + 1 mm.
95	.12 sec.	Normal	Normal	R_2 + 30. Also ? intraventricular block	T_1 − 2 + ½ mm. T_2 − 2 + 1 mm. T_3 + 1½ mm.
75	.15 sec.	Left, index +27	Normal	Normal	T_1 − 1 mm. T_2 − 1½ mm. T_3 + 1 mm.
98	.12 sec.	Normal	Normal	Normal high R_1 + 25. mm., S_2 − 8 mm.	T_1 flat. T_2 − 2 mm. T_3 − 1 mm.
Varying, 55 45 120 when regular	.2 sec. when P. is present	Slight left with regular rhythm. Index + 18	Small and notched when present	At first right bundle branch block. Later left bundle branch block. Still later reappearance of right bundle branch block	Varying as shown by plates from day to day: *a* T^1 sometimes − 10 mm. sometimes − 5 + 5 mm.; T^2 − 2 + 2½ mm.; T^3 + 9 to 10 mm. *b* T^1 begins high on downstroke of R, + 7 mm.; T^3 Also begins high and is + 8 mm.; T^3 − ½ to + 3 mm.
Regular at 55 Irregular at 80 or same as ectopic auric. rhythm	.12 to .18 sec. .2 to .05 sec. in *A-V* rhythm	Left, varying from index + 20 to + 30	Varying, ? isoelectric. Best seen in Lead III, sometimes + 1 mm., sometimes − 1 mm. Later inverted and − 1 mm. in both rhythms.	Slurring of upstroke of R_3	T_1 flat to + 1½ mm. T_2 + 5 to + 6 mm. T_3 + 5 mm.
80	.15 sec.	Right, index − 20	Normal	Normal	T^1 + 3½ mm. T^2 + 10 mm. T^3 + 7 mm. Long S^2 T^2 interval.
115	.18 sec.	Left, index + 38	P_2 notched	Wide, ? intraventric. block	T_1 − 2 mm. T_2 − 1 mm. T_3 + 1 mm. Later (two days): T_1 flat. T_2 + 1½ mm. Long S^2 T^2 interval T_3 + 1½ mm.
40 65	.18 sec.	Normal	P_2 notched P_2 normal	Normal	*a* T_1 + 3–1 mm.; T_2 + 7 mm.; T_3 + 2 mm. *b* T_1 notched + 1 mm.; T_2 broad + 1 mm.; T_3 flat.
Varying, 70 to 80	.12 sec.	Slight left, index + 18	P_2 low, + ½ mm. P_3 − ½ mm.	S_3 + 8 and slurred	T_1 + 4 mm. T_2 + 7 mm. T_3 + 4 mm.
90–100		Left, index + 19	Normal	Q–*R*–*S* normal	T_1 − 1 to + 2 mm. (varying on different days) T_2 − 2 to − 3 mm. T_3 − 3 to − 5 mm.
110	.19 sec.	Normal	P_2 notched, + 1½ mm.	S_1 and S_3 deep and slurred ? intraventricular block	T_1 + 4 mm. T_2 + 6 mm. T_3 + 2½ mm.

Four of the 12 positive cases showed definite *abnormalities of rhythm:* (1) Probable auricular standstill and idio-ventricular rhythm, later changing to auricular fibrillation and in a few days to normal rhythm just before death; (2) sino-auricular block with ventricular escape, later varying from an ectopic auricular rhythm to ventricular escape or to atrioventricular nodal rhythm; (3) marked sino-auricular bradycardia, possibly sino-auricular block; (4) variable sino-auricular block and auriculo-ventricular block with rare dropped beats.

The heart *rates* were variable, and the bradycardia commonly said to be present in uremia was not commonly observed in our series. A P–R interval of 0.2 second or over occurred in 2 cases. One of these cases had had digitalis as already discussed (Case No. 25). The P wave in Lead II was small and notched in four instances.

In 4 cases there was abnormality of the *QRS complex* indicating definite intraventricular block in 1 and probable intraventricular block in the other 3.

The *T wave in Lead II* was flat, diphasic or inverted in 7 of the 12 positive cases and unusually high (+ 5 mm. or greater) in the other 5 cases. In case No. 25 the T showed various queer forms, sometimes originating high on the downstroke of R_2 (see Fig. 4). In case No. 31 when the patient was quite sick shortly after admission to the hospital, the T_2 wave was + 7 mm. With the patient's gradual recovery the T_2 wave dropped to + 1 mm. Pronounced left axis deviation with an "index"[6] of + 18 or greater was present in 6 of the 12 positive cases; abnormal right axis deviation occurred only once.

Of these 12 cases with abnormal electrocardiograms 5 had slight to marked edema of the feet and legs and 1 had marked generalized edema. Seven had definite albuminuric retinitis; 3 showed normal fundi, was doubtful, and 1 was not examined. In 8 of the 12 cases a phenolsulphonephthalein kidney test was done; 4 showed no output in two hours and ten minutes; 2 showed 10 per cent or less and 2 showed 25 per cent in two hours and ten minutes; 7 had a hemoglobin reading of 75 per cent or less. All except 1 (Case No. 36) had the typical urinary findings of advanced nephritis. The systolic blood-pressure varied from 115 to 245 mm. of mercury with an average systolic blood-pressure of 202 mm. of mercury. The diastolic pressure varied from 82 to 160 mm. of mercury with an average of 132 mm. of mercury. In 11 of the 12 cases with abnormal electrocardiograms the non-protein nitrogen varied from 69 mgm. to 333 mgm. per 100 cc of blood, and 1 case (No. 13) had a urea nitrogen of 98 mgm. per 100 cc of blood. Of the 12 cases showing abnormality of electrocardiograms partially or wholly due to the toxic effects of uremia on the heart muscle, 11 died under hospital care and 1 was discharged "apparently improved."

There were 8 of the 38 cases of uremia studied, uncomplicated by heart disease or digitalis, which failed to show abnormality of the electrocardiogram. Two of these presented edema of the feet and legs and 1 showed rather marked edema of the face, thighs and legs. Three presented definite albuminuric retinitis, 3 showed normal fundi and in 2 the fundi were not examined. Five had no phenolsulphonephthalein excretion in the urine in two hours and ten minutes, 1 had a 25 per cent excretion and 1 a 50 per cent output. All of these 8 cases showing no abnormality of the electrocardiogram had a hemoglobin reading of 75 per cent or less. The systolic blood-pressure varied from 110 mm. of mercury to 210, with an average systolic pressure of 168 mm. of mercury. The diastolic pressure varied from 60 to 145 mm. of mercury and averaged 106.6 mm. of mercury. In 7 of the 8 cases where the determination was made, the non-protein nitrogen varied from 70 mgm. to 210 mgm. per 100 cc of blood, an average of 135.5 mgm. per 100 cc of blood. A comparison with 11 of the 12 positive cases in which a blood non-protein-nitrogen determination was made shows in the 11 positive cases a variation from 69 mgm. to 333 mgm. per 100 cc of blood and an average non-protein nitrogen of 143.4 mgm. per 100 cc of blood. The difference between the two groups is not striking enough and the cases not numerous enough to draw any conclusions. Finally, of the 8 cases of uremia failing to show abnormalities of the electrocardiogram 3 died under hospital care, 1 was discharged in "poor condition" and 4 were discharged temporarily "improved."

A review of these studies fails to show a common factor in either positive or negative group and the nature of the toxin causing the change in the heart muscle as well as any common factor is obscure. In general the positive cases seemed to have a more advanced nephritis, as apparently indicated by the hospital mortality, albuminuric retinitis, higher blood-pressures and apparently the greater incidence of edema. At present it is not possible by history, physical examination or laboratory findings to predict which cases of uremia will show abnormal changes in the form and direction of the electrocardiographic complexes.

A relatively high blood-pressure with a probable resulting hypertrophy occurred in most of the cases studied and left axis deviation occurred in 6 of the 12 positive cases, though not marked. These might be considered as possible factors in the changes produced in the *T* wave in some instances. However, a study of 14 cases of marked left-axis deviation, with an "index"[6] of from + 30 to + 45, showed the *T* wave in Lead II to be normal and upright in every instance. Twelve of these had T_2 waves of + $1\frac{1}{2}$ mm. to + 5 mm. Two had T_2 waves of + 1 mm., 1 of these having received an appreciable amount of digitalis. In this group the systolic blood-pressure varied from 115 mm. of mercury to 270 mm.

of mercury and the average was 185.8 mm. of mercury. The diastolic pressure varied from 70 to 150 and averaged 107.5 mm. of mercury.

Two cases of severe diabetic coma showed no abnormality of the electrocardiogram other than a tachycardia, the T_2 wave being upright and hormal.

Three cases showing abnormal electrocardiograms are presented in brief here.

Case Report.—Case I. C. C., a single man, aged twenty years, a checker in a rubber factory, entered the Out-patient Department of the Massachusetts General Hospital, January 17, 1923, complaining of rapid loss of vision.

About two and a half years before entrance the patient was found to have chronic nephritis at another hospital. This was discovered following an attack of influenza. He was unable to get insurance at this time because of the albumin in his urine. For two years he had practically no symptoms except severe "morning" headache occurring about once a week. There was complete absence of dyspnea and of edema of the feet. Three weeks before entrance to the Massachusetts General Hospital his vision started to fail and became progressively worse. He entered the hospital for this reason.

The past history reveals no story of rheumatic fever, chorea or scarlet fever. The tonsils were definitely bad in childhood and were removed at the age of eleven years. The past history was otherwise negative. There was no history or physical sign of venereal disease.

On *physical examination* the presenting features were as follows: a muddy pallor, an uremic breath, marked albuminuric retinitis and slight cardiac enlargement. The apex impulse of the heart was in the fifth interspace 8 cm. to the left of the mid-sternal line, and the mid-clavicular line was 7.5 cm.—very slight enlargement to the left clinically. There were no murmurs and no abnormalities of rhythm.

The blood-pressure was observed 4 times over a period of two months and the systolic pressure varied from 210 to 240 mm. Hg., and the diastolic pressure from 140 to 170 mm. Hg. The urine showed a large amount of albumin, granular casts and 6 to 12 red blood cells per high-power field. The non-protein nitrogen was taken 7 times in two months and varied from 70 to 111 mgm. per 100 cc of blood.

The patient was ambulatory although in a state of chronic uremia from January 17, 1923, to March 14, 1923, and was examined frequently in the hospital. After the latter date he was unable to come in but was confined to his bed at home with frequent vomiting attacks. Convulsions finally occurred and the patient died June 23, 1923, in uremic coma.

Discussion. A young man with chronic uremia was observed over a period of two months and blood nitrogen determinations were made and electrocardiographic plates taken. He received no digitalis at any time. There were never any signs of cardiac failure and cardiac

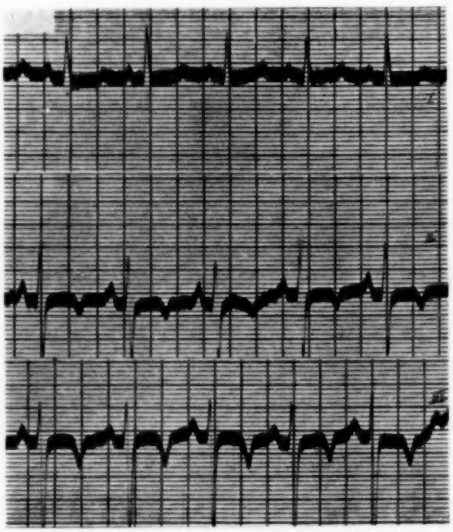

FIG. 1.—Electrocardiogram of C. C., taken January 31, 1923. Normal rhythm; inverted *T* in Leads II and III; slight left axis deviation.

FIG. 2.—Electrocardiogram of C. C., taken February 17, 1923. Normal rhythm; inverted *T* in Leads II and III; inversion of *T* in Lead II is more marked than in Fig. 1. Also *T* in Lead I is now inverted.

hypertrophy was only slight clinically. The *T* wave of the electrocardiogram in Lead II was definitely abnormal and was constantly inverted (See Figs. 1 and 2). The toxic effect of the uremia upon the heart muscle was probably the cause of this. The degree of inversion of the *T* wave bore no constant relation to the blood non-protein nitrogen.

Case II. G. S., a marine engineer, aged forty-three years, entered the Massachusetts General Hospital November 10, 1921, complaining of dyspnea. The symptoms were frontal headache and increasing dyspnea and weakness for eighteen months.

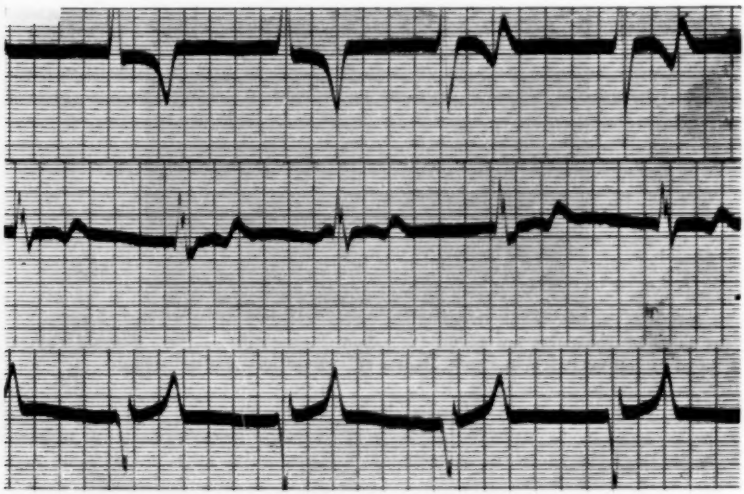

Fig. 3.—Electrocardiogram of G. S., taken November 18, 1921. Intraventricular block; no evidence of auricular activity; question of auricular standstill and idioventricular rhythm; varying ventricular complexes; *T* wave in Lead I varies from diphasic to inverted, according to shape of *Q R S*.

There was no history of rheumatic fever or chorea. No history or physical sign of venereal disease was present. The patient had received a total of the equivalent of 1.2 gm. of the dried digitalis leaf over a period of eleven days just before entrance. He received no digitalis while in the hospital.

The presenting symptoms and signs were stupor, cyanosis, albuminuric retinitis and medium moist rales at both lung bases posteriorly. The heart was markedly enlarged to both the right and left; the sounds were of fair quality and no murmurs were present. The systolic blood pressure was 200 mm. Hg. and the diastolic was 100 mm. Hg.

The urine showed a specific gravity of 1010 to 1012, a large amount

of albumin and occasional granular casts and white blood cells in the sediment. The non-protein nitrogen varied from 99 mgm. to 153 mgm. per 100 cc of blood. The blood Wassermann reaction was negative.

The patient grew steadily worse. The uremic symptoms became more marked, pericarditis with effusion developed and he died November 26, 1921.

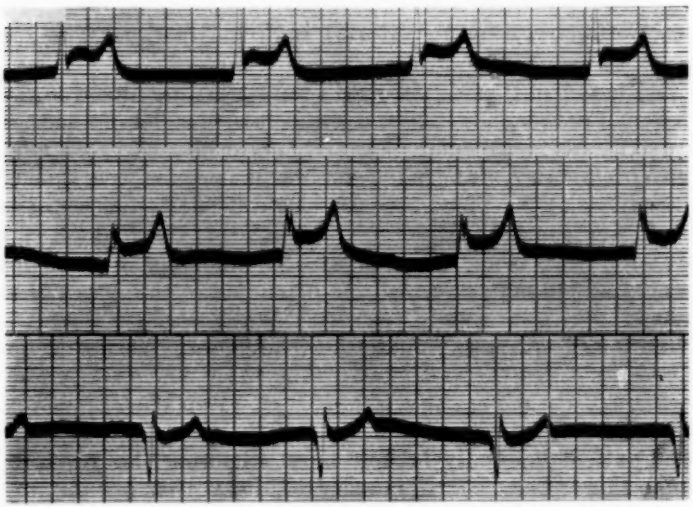

FIG. 4.—Electrocardiogram of G. S., November 22, 1921, still showing no evidence of auricular activity. Intraventricular block persists and the *T* wave in Lead II is high and now originates from the downstroke of the *Q R S* complex.

Discussion. The bizarre and rapidly changing electrocardiographic complexes (Figs. 3 and 4) cannot be explained by the ingestion of the equivalent of 1.2 gm. of digitalis leaves over a period of eleven days. Neither does hypertensive heart disease afford a complete explanation. The toxic effect of uremia on the heart muscle must be considered as the most likely explanation of the changes of the *Q R S T* waves. Digitalis may have been an additional factor.

CASE III. G. E., a white man, aged forty-three years, a druggist, entered the Massachusetts General Hospital, January 16, 1923, semistuporous with marked hyperpnea.

The patient had not been sick up to the present illness, which began two weeks before entrance with dyspnea on exertion. This gradually increased until he was obliged to go to bed. Three or four days before entrance his ankles began to swell and he began to grow drowsy. There had been some increase in urinary frequency

for two months, with nocturia once to twice a night during this period.

There was no history of scarlet fever, diphtheria, rheumatic fever or chorea during childhood. The past history was entirely negative so far as could be found out.

On examination the patient was pale, semistuporous, markedly hyperpneic and had a heavy urinous odor on his breath. Examination of the fundi showed papilledema, several small hemorrhages and one or two small spots of exudate on each side. Ascites was present; there were moist rales at both lung bases. There was marked edema of the ankles and over the sacrum.

Examination of the heart showed a left border of dulness of 11 cm. with a right border of 4.5 cm. and a midclavicular line of 8 cm. The heart sounds were irregular, slow and almost obscured by a loud to and fro friction rub. The radial and brachial arteries were thickened and tortuous. The blood-pressure was difficult to determine; the pulse beats came through very irregularly; the highest, a few beats, appeared below the cuff at 185 mm. mercury; all beats appeared at 140 mm. mercury; the diastolic pressure was 120 mm. mercury.

No urine specimen was obtained. The non-protein nitrogen was 173.5 mgm. per 100 cc of blood. The blood hemoglobin was 60 per cent and the red count was 2,370,000. Two Wassermann reactions proved to be negative.

The patient gradually became more stuporous, his respirations became slower and he died January 17, 1923, after one day in the hospital.

Subsequent autopsy showed a heart weighing 615 gm. with a normal looking myocardium. Acute pericarditis was present. There were no valvular lesions. Other findings were arteriosclerosis, arteriosclerotic nephritis, infarct of right lung, small infarcts of kidneys, right hydrothorax, slight ascites, chronic passive congestion, edema of legs and feet and ulcerative colitis.

Discussion. A man, aged forty-three years, with no evidence of syphilis, but quite toxic from advanced uremia, showed an unusual cardiac arrhythmia by electrocardiogram. Hypertension and cardiac hypertrophy with failure were present and also peripheral arteriosclerosis but there was no history of anginal failure. The arrhythmia was apparently due to a sino-auricular nodal depression with sino-auricular block (Fig. 5). Neither hypertensive heart disease nor arteriosclerosis explain this. The latter particularly is more likely to interfere with auriculo-ventricular conduction. The arrhythmia here is more likely due to a toxic effect of the uremia on the sino-auricular node. The equivalent of 0.3 gm. of powdered digitalis leaf over a period of seven days is not sufficient to produce such a toxic effect on the heart. Both the sino-auricular nodal depression and the

unusually high *T* in Lead II are best explained by the effect of the toxic products of uremia on the heart muscle (perhaps somewhat increased by digitalis).

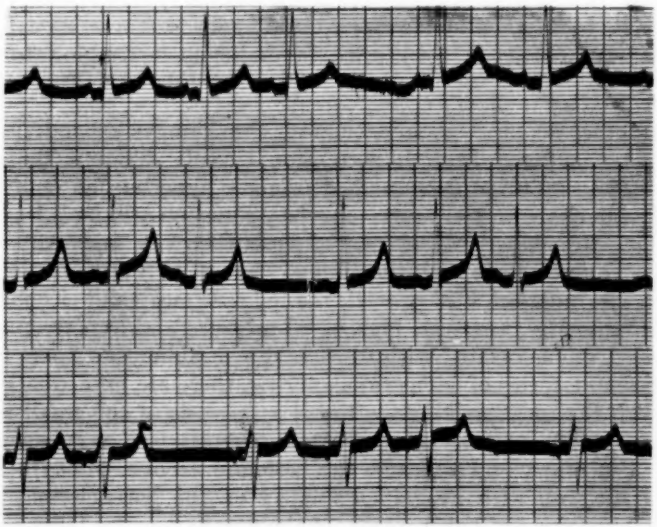

FIG. 5.—Electrocardiogram of G. E., January 16, 1923, showing sino-auricular block, every fourth beat "dropped" in Leads II and III. High *T* in Lead II and slight left axis deviation.

Conclusions. In certain cases of uremia and severe nephritis with an increased blood nitrogen there is a toxic effect acting in some respects like digitalis on the heart muscle. It may produce abnormal electrocardiograms: changes in the *T* wave of Lead II, less often abnormal rhythm, and rarely an increase in the auriculo-ventricular conduction interval* or in the duration of the *Q R S* complex.

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* Through the kindness of Dr. A. L. Barach of New York City we have received data concerning the electrocardiograms of a series of 20 cases of uremia observed by him. Seven of these cases were digitalized. Of the remaining 13, 8 showed diphasic or inverted *T* waves in lead II.

THE VASCULAR CHANGES OF THE KIDNEY IN HYPERTENSION.

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The microscopical examination of the kidneys of individuals who have suffered from hypertension reveals different findings. In a certain group of cases named primary hypertension or hyperpiesis, no changes are found in the kidneys (Allbutt,[1] Keylin,[2] Lee,[3] v. Monakow,[4] Moschcowitz,[5] Ophuels,[6] Vey and Allbutt[7]). This is in accordance with the clinical statement that in this group the renal function has proved normal (Strouse and Kelman[8]). More frequently, however, high blood-pressure and hypertrophy of the heart are associated with diseases of the kidneys. Apart from the different forms of glomerulonephritis, there are numerous cases in which the most striking feature is a sclerosis of the small renal arteries. The intensity of the arteriosclerosis is a very variable one. By comparison all stages can be found, from a slight thickening of the wall with insignificant effect on the parenchyma, to a hyaline occlusion of the majority of the renal arterioles followed by obliteration of the glomeruli, atrophy of the tubules and proliferation of the interstitial connective tissue. This sclerosis finally results in the well known clinical and anatomical picture of the primary contracted kidney (Gaskell,[9] Herxheimer,[10] Jores,[11] Loehlein[12]).

The question has frequently been discussed, whether the hyperplastic and degenerative changes observed in hypertension in the small arteries of the kidney are confined to this organ or whether other organs are also involved. Since the work of Gull and Sutton, the sclerosis of the renal arterioles has often been considered part of a universal arteriolar fibrosis (Jores, Moschcowitz, Muenzer[13]). Certain objections against a generalization of this assumption can be made, for there are undoubted cases of sclerosis of the small arteries confined to the kidney (Evans,[14] Herxheimer, Hecht, Loehlein). Where arteriosclerosis is found in the spleen, as well as in the kidney, it must be kept in mind that in this organ, arteriosclerosis is an almost physiological occurrence in the adult after forty to fifty years of age, (Herxheimer, Matsuno). In the cases with a more universal arteriosclerosis, the process in the kidney as a rule is more advanced and more pronounced than in brain, liver, testis, etc. Only in the kidney is this alteration followed by a well-characterized destruction of the parenchyma, whereas it is absent in the other organs just mentioned. In the pancreas,

however, the changes in the small arteries are sometimes almost as severe as in the kidney (Aschoff,[16] Herxheimer, Moschcowitz, Schwab[17]); here too, they may cause atrophy of specific tissue (islets), with clinical signs of disturbed function (diabetes—Hoppe-Seyler[18]).

It can be stated, therefore, that the small arteries of the kidney, in particular, are disposed to sclerosis. This local disposition may be partly due to the intricate vascular system of this organ apparently favoring circulatory disturbances, which, if they lead to an increase of the intravascular pressure, will cause changes in the vessels.

Can we observe changes in the arterio-capillaries of the kidney that will permit the conclusion that distinct circulatory disturbances exist? They should be sought only in cases of hypertension that are not far advanced. In the later stages, when the pathological process has advanced, the first and most characteristic consequence of an altered blood-flow will be overshadowed by secondary alterations. In other words, what are the presclerotic changes in the kidney.

Loehlein described marked dilatations of the arterioles preceding the sclerosis. According to him, the presclerotic dilatation gradually passes over to the thickening and degeneration of the arterial walls of the later stages. Loehlein's observation has been confirmed by Fahr. These two authors give no explanation for their findings.

During several years I have collected kidneys obtained in postmortems of cases with hypertension. In the present paper, the very beginning of the renal sclerosis will be mainly discussed.

From my collection I have chosen 5 cases of clinical hypertension of short or moderate duration. The determination of the exact time of onset is, of course, impossible because of the insidious character of the process, but a short review of the cases will indicate why I have selected these to illustrate the points under discussion. All 5 are males.

Case Abstracts. CASE I.—Aged twenty-seven years; sudden death.

Postmortem Findings. Heart 400 gm.; the opening of the left coronary artery closed by a fresh thrombus, 1 x ½ cm. in diameter. At the place where the thrombus was attached to the wall of the aorta, the intima showed slight fatty degeneration. Kidneys macroscopically normal.

CASE II.—Aged twenty-nine years; physician; smoked 60 to 100 cigarettes daily; he noticed that his blood-pressure was high (systolic 180) half a year ago; died suddenly.

Postmortem Findings. Heart 395 gm.; thrombosis of the left coronary artery; isolated sclerosis of the left coronary artery; kidneys hyperemic, of normal size and form.

CASE III.—Aged forty-five years; diabetes mellitus; systolic blood-pressure 190; no albuminuria; death in coma diabeticum.

Postmortem Findings. Heart, 390 gm.; pancreas 33 gm; extensive lipomatosis; kidneys (together), 302 gm.; cloudy swelling; slight hyperemia.

CASE IV.—Aged thirty-five years; symptoms of gout for a few months; systolic blood-pressure 200; died of influenza-pneumonia within twenty-four hours.

Postmortem Findings. Heart, 405 gm.; hemorrhagic pneumonia of the right lung; kidneys more consistent than normal and hyperemic.

CASE V.—Aged thirty-five years; house painter; blood-pressure 225. Clinical diagnosis: Chronic lead-poisoning; primary hypertension; hemorrhage of brain.

Postmortem Findings. Heart, 557 gm.; thrombosis of the arteria basilaris cerebri; distinct sclerosis of the basal arteries of the brain; kidneys firm, smaller than normal (weight together 215 gm.), surface smooth.

Microscopical Examination. Examining the tissues of Case I microscopically, I first had the impression that the kidneys were normal; but later I changed my opinion, after I had learned, by comparison with other cases, to recognize an alteration which at first sight was not very striking. This was a slight and circumscribed dilatation of the afferent arterioles. Also in Cases II, III and IV, the lumen of the vasa afferentia was distended more distinctly, especially in Case III.

As shown in Fig. 1, the dilatation begins at the hilus of the glomerulus. The short intraglomerular part of the arteriole, which normally forms a small ampulla, is at first widened. Later, the whole vas afferens is dilated (Fig. 2).

In the earliest stage, the structure of the vascular wall apart from the distension is not affected. As the alteration proceeds, the walls become thicker by proliferation of the cells of the intima and enlargement of the cells of the media (Fig. 3). Hyaline masses appear under the endothelium (Fig. 2). They spread out over the intima and to the adjacent part of the media. Finally the vascular coats are completely involved, while the lumen becomes markedly narrowed. This stage was reached in Case V (Fig. 4).

In the other organs—brain, pancreas, liver—no sclerosis and no dilatation of the smallest arteries was found. This excludes the possibility that the dilatation of the renal arterioles is merely a part of a universal passive congestion. Besides, in this condition the vasa efferentia with the tufts of the glomeruli and the veins are distended, but not the vasa afferentia.

The isolated dilatation of the afferent arterioles of the kidney in

FIG. 1.—Dilatation of the intraglomerular part of the vas afferens. Irregular blood content of the tufts. Beginning hyaline degeneration of their wall (Case III).

FIG. 2.—Dilatation of the vas afferens with hyaline degeneration of the intima. Irregular blood content and more advanced hyaline degeneration of the tufts (Case III).

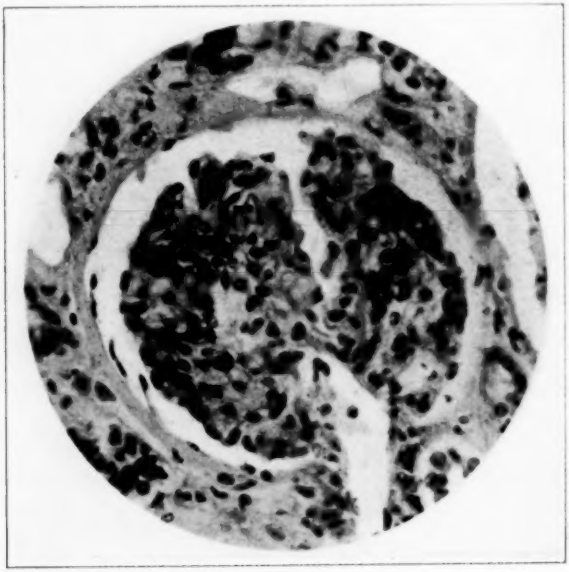

FIG. 3.—Dilated vas afferens with proliferation of the cells of the wall. Thickening of the Bowman's capsule (Case IV).

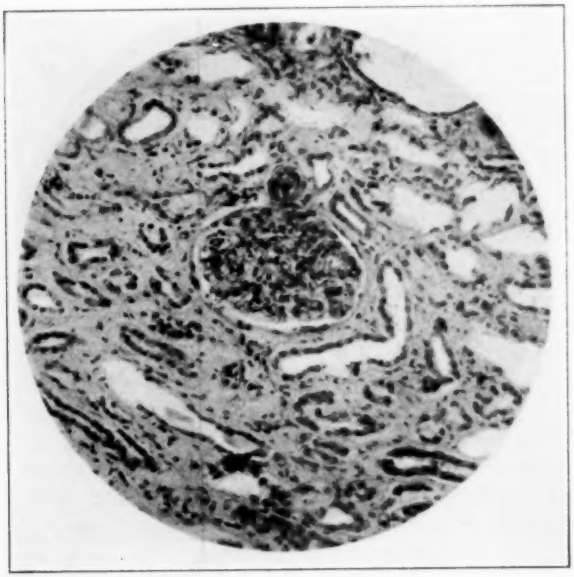

FIG. 4.—Hyaline sclerosis of the vas afferens with pronounced narrowing of its lumina (Case V).

early hypertension is interesting because it indicates not only disturbances in the renal circulation, but it points to a certain place where the disturbances may arise.

When we find a circumscribed dilatation of a portion of a vascular system without structural alteration of the wall, we must assume that a narrowing of the lumen has occurred at a point beyond the dilatation with a resulting increase in the pressure in the proximal portion. Such pressure distends the wall.

Distal to the vasa afferentia are the tufts of the glomeruli. The splitting up into the numerous tufts produces a sudden and considerable increase in the vascular capacity. Under normal conditions we should therefore anticipate no resistance to the circulation at this point.

Are changes to be found in the tufts of the glomeruli in the presclerotic stage? According to Loehlein, the glomeruli are normal at this time.

Case I of our series seemed to confirm Loehlein's statement, for no alterations of the glomeruli were noted. In the other cases, however, the glomeruli could not be called normal. Irregularities were found in the blood content of the loops, and in the same glomerulus, some tufts were filled by blood, while others were empty and narrowed. The capillary walls appeared to be thickened and less distinctly stained. In Case III these irregularities were well pronounced and combined with circumscribed hyalinization of the capillaries (Figs. 1 and 2). In Case IV, thickening of Bowman's capsules was also observed, (Fig. 3). We are therefore able to state that in the early stages, in which the vasa afferentia are dilated, changes in the glomeruli may be seen. These changes, called by Moschcowitz "arteriosclerosis en miniature," cannot be considered as resulting from the sclerosis of the arterioles, as was done by several authors; first, because the hyalinization is sometimes more advanced in the tufts of the glomeruli than in the afferent vessel, and secondly, because in the beginning there is often no connection between the degenerated parts of the glomerular capillaries and the arterioles. Thus, the hyaline thickening is quite frequently found first at the top of a tuft. Evans and Dunn also are inclined to regard the glomerular changes primary to those of the small arteries. It is not to be denied, of course, that the narrowing and the occlusion of the lumen of the vasa afferentia, found in the later stages of genuine atrophy of the kidney, means severe damage to the glomeruli (Jores, Loehlein).

The hyalinization of the capillaries just described, cannot form the real cause for the increase of pressure within the arterioles, for it was absent in Case I, though the afferent vessels were distended. But, in my opinion, the sclerosis of the tufts indicates a direct injury to the glomeruli. It is very likely that this injury first leads to contractions of the capillary tufts without destruction of their wall.

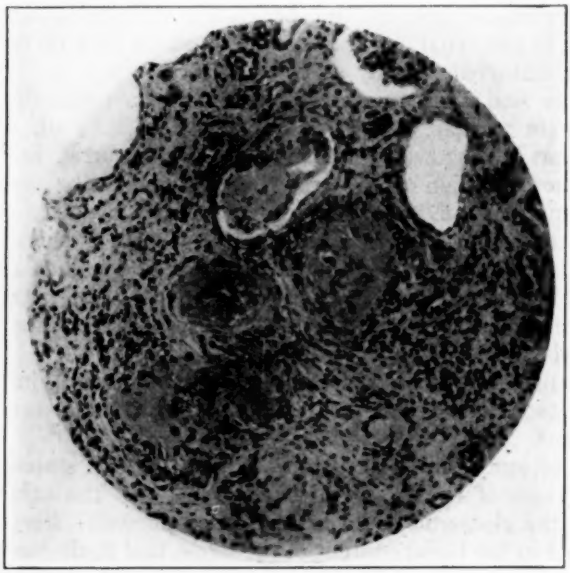

FIG. 5.—Necrosis of renal arterioles in syphilis.

FIG. 6.—Dilatation of the vas afferens in chronic glomerulonephritis. Man, aged forty years. Heart: 465 gm. Secondary contracted kidney.

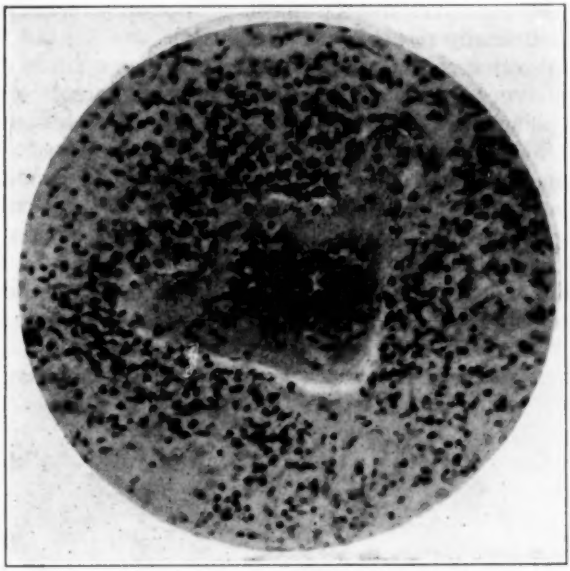

FIG. 7.—Arteriolitis with necrosis in subacute glomerulonephritis. Man, aged twenty-six years. Heart: 385 gm.

FIG. 8.—Very severe arteriolitis in acute exacerbation of chronic glomerulonephritis.

If the injury continues and the spasm is frequently repeated, visible changes will finally result in the capillaries.

By contraction of the tufts the blood flow through the glomeruli will be interrupted. The irritating agent, held back by the spasm in the capillaries, will accumulate in the arterioles, bringing about here the effort of contraction and this against an increased resistance. As the muscular coat of the vasa afferentia are too insignificant to compensate successfully for this increase in work, other parts of the circulatory system will react to keep up the renal circulation, and at the point of resistance, the thin walls of the afferent arterioles will be distended. This explanation presupposes the existence of an independent contractility of the capillaries.

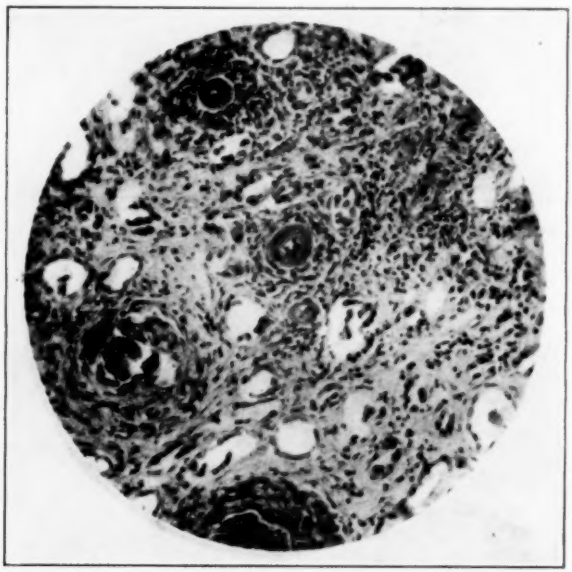

FIG. 9.—Arteriolar sclerosis in the same kidney as Fig. 8.

Extensive investigations made during the last few years seem to have proved beyond doubt that the capillaries may contract and dilate without any influence from the vessels between which they are intercluded. For details, reference should be made to the funddamental works of Krogh,[20] Dale, [21] Ebbecke,[22] Cotton, Shade and Levin,[23] and Mueller.[24] Most of this work has been carried out on the capillaries of the skin, which may readily be studied during life. Relations between the capillaries of the skin and those of the kidney have also been suggested (Weiss,[25] Schlayer,[26] Eskil Kylin[27]). Direct observation of contractions of glomerular capillaries in the frog kidney has recently been reported by Richards.[28]

Though an independent contractility of the glomerular capillaries in man has not yet been directly proved, these observations, combined with the microscopical findings in the renal arterioles in early hypertensions, give strong support to its existence. The capillary spasm will first affect the circulation of the kidney. But the sudden and repeated elimination of an important part of the circulatory system will not remain without effect on the heart. Its reaction against the increased resistance will be an increased action. Hence the blood-pressure will rise.

In explaining essential hypertension, spasmodic contractions of the peripheral vascular structure, especially of the small arteries, have been frequently emphasized (Monakow, Pal,[29] Schlayer, Strouse and Kilman, Volhard,[30] Warfield). With regard to the kidney, the isolated dilatation of the vas afferens, as found in early hypertension, rather suggests spasms of the tufts than of the arterioles.

The arterio-capillary contractions may not be confined to the kidney, for they may also occur in other parts of the body. It will easily be understood, that disturbances mainly in the renal blood flow may play an important role in altering the blood-pressure, when we consider the rich blood supply and great functional activity of this organ (v. Monakow, Warfield).

While it is supposed that capillary contractions cause the rise of the arterial pressure, the dilatation of the vas afferentia is to be regarded as resulting from the hypertension. Does the latter also produce the sclerosis which follows the dilatation?

The theory has been brought forward that arteriolar sclerosis arises from hypertension by Allbutt, Faber, Moschcowitz,[33] and others. But the height of the blood-pressure does not correspond to the intensity of the vascular degeneration. There are cases showing the same increase of the pressure, but the changes in the renal arterioles are widely different. Severe hyaline and lipoid destruction of the small arteries is sometimes found combined with a blood-pressure and a weight of the heart less than in benign vascular sclerosis of the kidney. A type of renal arteriosclerosis is characterized by a blood-pressure which is almost normal (Ophuels, Lichtwitz[32]).

Therefore, we cannot but assume that certain irritants directly affect the vessel wall. It is very likely that such substances are those which cause the spasm of the glomerular tufts, and accumulate in the precapillary part. On the intensity of the direct irritation will depend the extent of the sclerosis.

As to the nature of this irritant, attention is directed in this connection to lead and nicotine[34] (Cases II and V), both of which are known to induce vascular contractions. One needs but to recall the arterial spasm of lead colic; and, according to Naegeli,[35] the paleness of lead miners is usually due to vascular spasms in the skin, and not to anemia.

The relative frequency of genuine atrophy of the kidney in cases of diabetes and gout, indicates that toxins affecting the small arteries are produced in disturbed metabolism. The nature of these toxins has not yet been defined. Aufrecht[36] suggests, from his studies in guinea-pigs, that the abnormal concentration of uric acid is injurious to the arterioles. In a series of experiments, I injected solutions of mono-sodium urate intravenously into 5 rabbits, each receiving 5 to 10 mg. of urate daily for four to six weeks. There were no symptoms of disturbed kidney function to be observed. In the urine, albumin and casts were absent, and the urea, non-protein nitrogen- and creatinin-content of the blood was normal. The uric acid soon disappeared. The rabbits were killed later. The kidneys showed no pathological changes. These experiments, however, have no bearing on disturbances of the purin metabolism in man, the latter being so different in this regard from the small rodents used in laboratory work.

In some cases relations have been suggested between cardio-renal diseases and disturbances of the internal secretion (thyroid, A. Fischberg[37]) Munk and Newburgh,[38] emphasize the deleterious influence on the arterial wall of diets rich in proteins.

May hypertension and arteriolar sclerosis result from injuries of an infectious nature? Goepp,[39] made reference to the possibility of focal infection being responsible for a certain number of cases of hypertension. The theory has been advanced by several investigators (Klotz, Ophuels), that in arteriosclerosis an inflammatory factor participates. Ophuels lays stress upon the close etiological relationship between infection and arteriosclerosis. I have seen typical genuine atrophy of the kidney connected with chronic tuberculosis of bone.

Fahr and Meyer[40] have described in primary contracted kidneys very severe alterations in the small arteries, with necrosis and inflammatory destruction of the vascular wall. According to these authors, syphilis and rheumatic arthritis play an important role in the etiology of these cases.

In Fig. 5 such severe changes in the renal arterioles are shown. These appeared in a man, aged thirty years, who came to the hospital complaining of shortness of breath and pains in his chest. He admitted a syphilitic infection about three years ago. The Wassermann test was strongly positive. His systolic blood-pressure was 200. Albumin and many waxy casts were found in the urine. The patient died suddenly of heart insufficiency before an exact clinical examination had been made. The postmortem revealed: Hypertrophy of the heart, (weight 480 gm.); severe sclerosis of the coronary arteries; no atheroma in the aorta. Spleen: weight 204 gm., Kidneys: weight, 100 gm., with surface coarsely granulated, cut surface pale, grayish-red, structure less distinct and consistency increased. In the microscopical examination of the kidneys,

hyaline and lipoid degeneration of the arterioles was found. Some small arteries were necrotic with structureless walls. There was only a slight inflammation around the necrotic vessels. Many glomeruli revealed hyaline degeneration. In some of the remaining glomeruli, necrosis of single loops was seen.

The histological picture of this kidney fully resembles Fahr's and Meyer's descriptions. But I hesitate to include these changes in the groups of sclerotic diseases of the kidney. There is certainly not always a definite demarcation between arteriosclerosis and inflammation. A cellular reaction, however, like that described, ought rather to have been recorded as specific arteritis than as arteriosclerosis (Cp. Aschoff).

Affections of the renal arterioles, similarly intensive sometimes occur in glomerulonephritis. In this connection, a brief discussion of the findings in the small arteries in nephritis may be of interest. Here we deal with an evident obstruction of the glomerular circulation by the inflammatory reactions within the tufts. Does this obstruction lead to vascular changes like those described in hypertension?

From numerous studies it is known that in cases of nephritis the vasa afferentia are often altered (Gaskel, Loehlein, Dyke[41]). Aufrecht[42] and Elwyn,[43] therefore, emphasize the importance of these as primary lesions in these diseases. Aufrecht described thickening of the wall, swelling of the nuclei of the muscle cells, and an increased number of cells in the adventitia. Ophuels called attention to an early subendothelial thrombosis of the small arteries, followed by fibrosis as a result of organization. Loehlein mentioned the fact that the vasa afferentia were often dilated. In 10 to 20 per cent distinct alterations of the walls were present. He found necrosis and formation of small aneurysms. Loehlein's observations were confirmed by Fahr. Baehr and Sacks[44] have seen severe lesions in the small arterioles occurring in diffuse glomerulonephritis combined with verrucous endocarditis. Bell and Hartzel[45] mentioned thrombosis of the affected arterioles.

In 94 cases of acute and subacute glomerulonephritis which I examined, dilatation of the vasa afferentia was very common. Sometimes this was of moderate extent, occasionally very pronounced (Fig. 6). The resemblance of the dilated vasa afferentia in Figs. 2 and 6 is very striking. In Fig. 6 the tufts of the glomeruli are distinctly closed by inflammatory changes in their wall. Five times I observed very marked alterations of the arterioles. They were necrotic, surrounded by leukocytes and lymphocytes which invaded the structureless wall and filled the lumen (Figs. 7 and 8). This arteriolitis could not be due to mechanical injury (stasis, pressure), but must be the result of a distinct toxic irritation.

In the chronic forms of glomerulonephritis (secondary contracted kidney), hyperplastic sclerosis is frequently found in the small

arteries. Loehlein separates this sclerosis from the acute arteriolitis. The former is considered by him as due to the high blood-pressure. But the increased pressure cannot in itself produce the vascular change, for we see cases of chronic glomerulonephritis with sclerotic arterioles and without hypertrophy of the heart (Evans).

In the kidney from which Fig. 6 was taken, there were, besides the acute inflammatory changes, older processes that showed more or less advanced obliteration of the glomeruli, and atrophy of the tubules. The different age of the inflammatory attacks was very marked. A typical hyaline sclerosis had developed in the areas of chronic inflammation (Fig. 9), while the arteriolitis was confined to the areas of acute inflammation. This can be explained on the assumption that the arteriolitis and the sclerosis were produced by similar causal agents, the former being the result of a very intensive and acute toxic alteration; the latter being due to a less severe and chronic affection.

From these observations a distinct resemblance of the vascular changes in the primary sclerosis of the kidney to those in nephritis can be determined. This is the reason why the two conditions, though different in their nature, have often been confused. The resemblance lends support to the theory I have advanced above in an effort to explain the genesis of the isolated renal arteriosclerosis in hypertension.

Conclusions. No satisfactory explanation has yet been given for the frequent coincidence of hypertension, hypertrophy of the heart, and sclerosis of the small arteries of the kidney. That the sclerosis may cause the rise of the blood-pressure by increasing the resistance in that part of the circulation has been denied. Of the objections brought forward against this theory, the most important one is that hypertension may occur though the renal arterioles show no thickening of their wall. For these reasons it was thought that the hypertension was primary and it induced the changes in the vessels. In proof of this conception, it has been emphasized that the sclerosis is not confined to the kidney, but represents a universal affection of the arterioles. But this explanation is not convincing either; because the height of the blood-pressure does not correspond to the intensity of the vascular changes; because the universal arteriolar fibrosis is not as pronounced nor as constant as it has been declared to be. There are many cases with an isolated sclerosis of the small arteries of the kidney. If other organs are also affected, the process in the kidney, as a rule, is the most advanced one.

In recent times, arterial spasms have been brought in causal connection with the hypertension. There is a distinct tendency to be noted to localize these spasms in the peripheral part of the vascular system. Some authors speak of contractions of the arterioles, while others point toward the capillaries (Warfield, Muenzer).

Though these contractions may be universal, they become most significant in the kidney because of the peculiar vascularization of this organ. Based upon the microscopical findings in the kidneys in early hypertension, I would suggest that the primary renal lesion should be sought in the tufts of the glomeruli. The fatal spasms occur in these. They result in a sudden interruption of the glomerular circulation and in an increase of the pressure in the afferent arterioles. The increased pressure distends the arteriolar wall. This is the first change remaining visible after death. Later the tufts, too, show signs of the harmful irritation. Their blood content becomes irregular. The capillary walls appear to be thickened and undergo hyaline degeneration (capillary sclerosis).

The afferent arterioles are not only exposed to the rise of the pressure in their lumen, but irritating matter of endogeneous or exogeneous origin will also accumulate in that part of the arterial system, and act most intensively upon its wall. As a result of this direct toxic injury to the arteries, we find in the later stages proliferation of the intima, hyaline and lipoid degeneration. The differences in the extent of the degenerative changes can be readily explained by the different quality and intensity of the injurious agent.

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PITFALLS IN THE DIAGNOSIS OF DIABETES.

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Urine Analysis in Diabetes. That urine analysis alone is not a sufficient criterion in the diagnosis of diabetes, has been emphasized in various previous publications,[1] in which it has been pointed out that the presence of sugar in the urine informs us only that the renal filter is permeable to glucose, and that moreover it does not identify the level of glucose concentration in the blood at which the kidney in any individual case becomes permeable. The presence of glycosuria merely gives us a lead—a suggestion that the investigation should be carried further in order that the primary cause of the glycosuria may be established.

Glycosuria may be caused by any of the following conditions: (1) A low renal threshold; (2) a heavy carbohydrate meal; (3) diabetes mellitus. If in any case it is found that the glycosuria is due to one of the first two of these causes, it can be disregarded. It is obviously of prime importance, therefore, to be able to identify those cases in which the glycosuria is an indication of the third condition, that is, when it is due to diabetes.

When sugar in the urine is detected by the ordinary laboratory tests, (there are traces of sugar in the urine at all times, but in such a low concentration that it is not detectable by the ordinary laboratory tests), it is due to the fact that the blood-sugar concentration has been raised above the renal threshold for that case. As long as the blood-sugar level stays above this renal threshold there

[1] Methods of Precision in Diagnosis of Diabetes, a New Instrument, Jour. Am. Med. Assn., 1921, **78**, 103; Differential Diagnosis of Diabetes by Means of Glucose Tolerance, Jour. Am. Med. Assn., 1922, **79**, 1234; Interpretation of Blood-sugar Estimations that are Near the Normal, Jour. Lab. and Clin. Med., 1922, **8**, 145; Diabetes and Life Insurance, Atlantic Med. Jour., 1923, **26**, 539; Differential Diagnosis of Diabetes, Am. Jour Med. Sci., 1922, **166**, 275; One Relation of Glycosuria to Kidney Permeability, Endocrinology, 1923, **7**, 699.

will be an active excretion of sugar into the urine; when the blood-sugar level falls below this point, the excretion will cease. It is evident that if the threshold of renal permeability were at about the same level in all normal individuals, it would be a comparatively simple matter to establish the interpretation of glycosuria in any given case. Unfortunately, however, the renal threshold varies widely in normal individuals as well as in diabetics. (Table I.)

TABLE I.—VARIATIONS IN KIDNEY PERMEABILITY.

Cases showing normal glycemia with glycosuria.		Cases showing hyperglycemia without glycosuria.	
Blood sugar, mg., per 100 cc.	Number of cases.	Blood sugar mg., per 100 cc.	Number of cases.
40– 50	1	120–130	13
50– 60	6	130–140	10
60– 70	3	140–150	9
70– 80	20	150–160	4
80– 90	14	160–170	5
90–100	17	170–180	4
100–110	22	180–190	2
110–120	13	190–200	1
120 and up	2	200–210	4
		210–220	1
		220–230	1
		230–240	2
		240–250	1
		250–300	1
		300–350	1
		350 and up	0

It is due to this fact that a patient, and often a doctor as well, is perturbed by the fact that one doctor has found glycosuria and another has not, even though both examinations may have been made on the same day. The patient who because of such a disagreement on the part of two physicians has sought further help invariably inquires, "Are such different findings possible or were both or either due to a faulty test?" "It is quite possible that both physicians were right," I usually reply, basing my judgment upon such findings as those shown in Chart I. In the case of the patient whose blood-sugar curve is shown in this chart, blood-sugar estimations and urine examinations were made hourly from 8 A.M. to 4 P.M. The patient ate a moderate breakfast at 8 o'clock and lunch at 12. The chart shows that the sugar appeared in the urine when the blood-sugar concentration was 150 mg. per 100 cc. In other words, when the blood-sugar level reached 150, there began to be an active excretion of sugar, a sort of overflow into the urine. Charts II and III show a like sequence of events in a diabetic patient; namely, each meal was followed by a rise in blood-sugar with the resultant appearance of glycosuria. We may conclude that in every individual the blood stream is flooded with sugar for a shorter or a longer period after a meal, depending on the tolerance of the individual for carbohydrates, the fasting blood-sugar level in a normal individual being reached within one to two and a half hours, in a diabetic, within

six to nine hours. As far as the blood-sugar content is concerned, therefore, the difference between a normal individual and a diabetic is that in the normal individual after each meal the blood-sugar

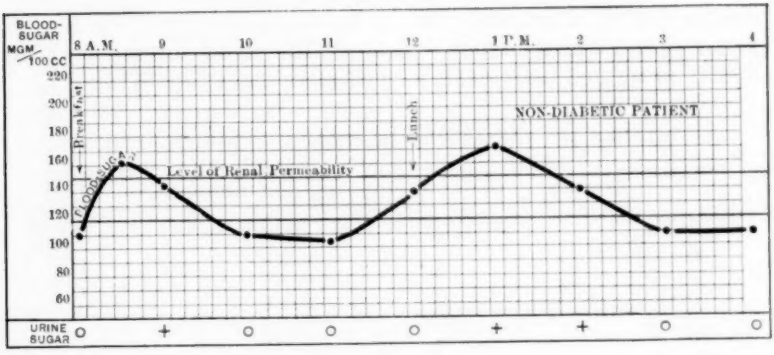

CHART I

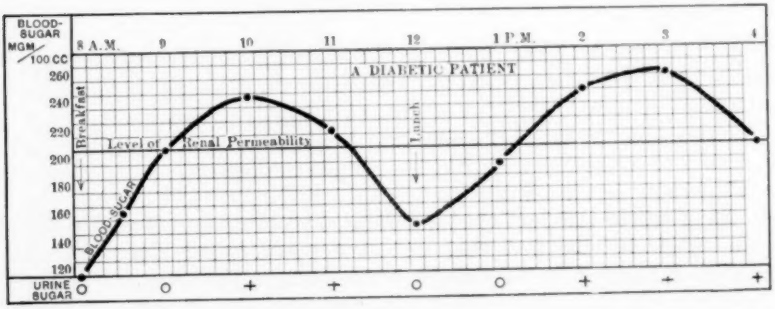

CHART II

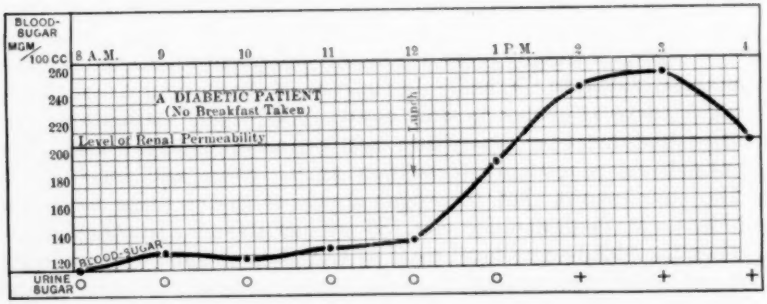

CHART III

content is somewhat increased for a short time whereas in the diabetic the blood-sugar rises to a higher level, which persists for a much longer time. Another point noted in a study of Chart I is shown by the following figures:

	A. M.				M.	P. M.			
	8	9	10	11	12	1	2	3	4
Blood sugar mg. per 100 cc.	110	146	110	106	140	172	140	110	110
Urine sugar	Neg.	Pos.	Neg.	Neg.	Neg.	Pos.	Pos.	Neg.	Neg

It will be noted that at 9 A.M. the urine examination was positive although the blood sugar was below the permeability level. This might have been misinterpreted had we not made an examination at 8.30, a half hour after breakfast, when the blood sugar was above the permeability level. The chart shows that for thirty-five minutes the blood-sugar content was above the renal permeability level so that during this period there was an active excretion of sugar into the urine. For that reason we find glycosuria at 9 o'clock, although the actual blood-sugar figure apparently does not warrant it. A similar finding, impossible of correct interpretation by itself alone, is shown at 2 P.M. A proper interpretation of glycosuria therefore demands also a knowledge of the blood-sugar level at the time the preceding specimen was voided. If the blood sugar at that or any intervening time was above the renal threshold, glycosuria will surely be found; for the urine collected represents not only the urine secreted at the time the specimen of blood is taken, but also that secreted during a preceding period of from two to six hours. This fact explains why among the 9 urine examinations, glycosuria was found in 3 of them. It is obvious that if this individual had been examined at 10 o'clock by one physician and at 2 by another physician, there would have been conflicting opinions.

Chart II shows the blood-sugar curve of a diabetic in whom the kidney permeability level was as one would expect much higher than in the non-diabetic patient, namely, at 210 mg. per 100 cc. The morning blood-sugar was normal, as it can be in most diabetics under proper treatment. As shown in the chart synchronous examinations of blood and urine, were as follows:

	A. M.				M.	P. M.			
	8	9	10	11	12	1	2	3	4
Blood sugar mg. per 100 cc.	120	210	248	222	156	198	259	262	210
Urine sugar	Neg.	Neg.	Pos.	Pos.	Neg.	Neg.	Pos.	Pos.	Pos.

Thus among 9 urine examinations, glycosuria was found 5 times. In this case also had the patient had urine examinations made by two different physicians one at 10 o'clock and the other at 1 o'clock he would have obtained two conflicting opinions; further, as is shown by Chart III, six successive examinations on the following day, on which the patient had no breakfast would each have shown no sugar. What final conclusion could be drawn from these urine tests alone? The proper interpretation of the case is evident only when the results of the urine examinations are considered together with the blood-sugar estimations.

The above considerations of the possible variations in urine sugar content show clearly the folly of attempting to interpret a single urine finding, whether it be positive or negative.

Single blood-sugar estimation. If blood-sugar estimations are to afford any dependable information they cannot be taken at random. The result of a single blood-sugar estimation may be worse than nothing if the possibility of a postprandial hyperglycemia for example is not taken into consideration. Thus Chart I shows that at 1 o'clock in the afternoon the blood sugar was 172 mg. per 100 cc and sugar was found in the urine. Such findings might easily be interpreted as indicating a diabetic condition. Yet, in these cases as is demonstrated by the chart, nothing would be further from the truth. Again in Chart III a judgment based solely upon the low blood-sugar estimation of 128 mg. per 100 cc and the aglycosuria would lead to the conclusion that the person is not a diabetic, a dangerous judgment for the patient in view of the testimony of the whole chart.

It follows that just as a single urinary examination does not justify a diagnostic conclusion, so also a single blood-sugar examination with a synchronous urinary examination does not justify a diagnostic conclusion.

Fasting blood sugar alone and blood sugar taken three hours after a heavy carbohydrate meal. A fasting blood-sugar estimation with a urine examination alone does not offer us sufficient information upon which to base a diagnosis in all cases. If the fasting blood-sugar content is high, then the patient is certainly a diabetic whether or not there is glycosuria. But if the fasting blood-sugar content is normal or near normal, whether or not glycosuria be present, we cannot, on the other hand, say that the patient is not a diabetic. If we bear in mind that with the proper diet the fasting blood-sugar content of any diabetic may be normal, then we shall hesitate to base an opinion solely on a low fasting blood-sugar estimation.

This point is illustrated by Table II which shows fasting blood-sugar estimations and urine analyses in 41 diabetic cases with blood-sugar estimations and urine analyses in each case three hours later after a heavy carbohydrate meal. Although some of these cases were mild and others severe, in only 1 case was the fasting blood-sugar more than 130 mg. per 100 cc; in 28 cases it was below 120 mg. per 100 cc. The table shows that in every case the fasting blood-sugar content was normal but at the end of the three-hour period after the ingestion of a heavy carbohydrate meal, hyperglycemia was present. In spite of this uniformity in the blood-sugar findings at the beginning of the test, some started with no glycosuria and had none at the end; others started with no glycosuria and ended with glycosuria; others started with glycosuria and ended with no glycosuria; and others started with glycosuria and ended with glycosuria. With such a variation in the urinary findings it would be hard indeed to interpret the presence or absence of diabetes from the urinary findings alone.

TABLE II.—VARIATIONS IN GLYCOSURIA-GLYCEMIA RELATIONSHIP IN DIABETICS.

		Fasting.		Three hours after heavy carbohydrate meal.		
	No.	Blood sugar, mg. per 100 cc.	Urine sugar.	Blood sugar mg. per 100 cc.	Per cent increase.	Urine sugar.
Glycosuria: Fasting, no; at 3 hrs., no	1	115	Negative	135	17	Negative.
	2	105	"	145	35	"
	3	108	"	139	29	"
	4	84	"	155	84	"
Glycosuria: Fasting, no; at 3 hrs., yes	5	117	"	297	154	Positive.
	6	104	"	193	85	"
	7	105	"	150	42	"
	8	126	"	226	71	"
	9	132	"	467	253	"
	10	124	"	454	266	"
	11	84	"	457	344	"
	12	126	"	426	238	"
	13	99	"	297	200	"
	14	129	"	405	213	"
	15	117	"	587	401	"
	16	91	"	300	229	"
	17	130	"	294	126	"
	18	95	"	138	45	"
	19	78	"	141	80	"
	20	115	"	222	93	"
	21	108	"	261	141	"
	22	109	"	206	88	"
	23	98	"	192	95	"
	24	118	"	306	159	"
	25	97	"	191	96	"
	26	65	"	175	169	"
	27	95	"	185	94	"
	28	130	"	246	89	"
	29	107	"	142	32	"
	30	129	"	308	138	"
	31	98	"	142	44	"
	32	122	"	199	63	"
	33	103	"	172	66	"
Glycosuria: Fasting, yes; at 3 hrs., no	34	109	Positive	184	68	Negative.
Glycosuria: Fasting, yes; at 3 hrs., yes	35	117	Positive	199	70	Positive.
	36	130	"	214	64	"
	37	122	"	164	34	"
	38	120	"	178	48	"
	39	126	"	460	265	"
	40	70	"	380	442	"
	41	117	"	189	61	"

In the first group the lack of glycosuria at the end of the three-hour period means simply that the blood-sugar content did not rise at any time between the first and the second examinations.

The presence of glycosuria in the last examination of the second group of cases is readily understood as the blood-sugar content in each at the end of the period reaches above the renal threshold.

The single case in the third group requires a special examination to discover the reason for the apparently paradoxical finding. To start with a blood sugar of 109 mg. per 100 cc with glycosuria, and to end with a blood sugar of 184 mg. per 100 cc with no glycosuria, would seem at first glance, to be an error. An examination

of the successive blood-sugar estimations will explain the apparent anomaly:

	Fasting.		1 hour later.	2 hours later.	3 hours later.	4 hours later.
Blood sugar, mg. per 100 cc	109	Heavy carbohydrate meal.	309	348	184	122
Urine sugar . . .	Pos.		Pos.	Pos.	Neg.	Neg.

There is glycosuria at 309, also at 348. The urine quantity at the one-hour period was very small, only 35 cc, and consequently it must have been very concentrated, so that even a small quantity of sugar could be detected by the ordinary test. There is no glycosuria at 184; this sample was larger in quantity, however (450 cc), so that a small quantity of sugar would be so diluted that it might escape recognition by the ordinary tests, even though it would be recognized in a concentrated urine. At the four-hour period the urine is still negative at 122; yet at the start it was positive with a blood-sugar level of only 109. How can we account for this?

Only one explanation seems possible, and that is the possibility of a high postprandial blood-sugar following the evening meal. If, as in this case, this figure was somewhere near 348, there would follow a gradual drop from 348 to 109 but the concentrated morning specimen would still contain the sugar from the high level, for urine always tells the whole blood-sugar story from the time of the last voiding. This would explain the glycosuria at the fasting blood-sugar level of 109 and its absence at 184 mg. per 100 cc.

The fourth group presents the obvious picture of severe diabetes, a clear cut picture of high hyperglycemia with resultant glycosuria.

These cases show what varied combinations of hyper- and hypoglycemia with aglycosuria and glycosuria are possible. The explanation of each combination is not difficult when all the data are at hand, but it is often impossible without the complete picture.

Blood-sugar examinations by the micro method. Clinicians depend for their information upon their laboratory technicians. A technician who is well trained should be able to do equally good work with different methods. Two years ago, I tried such an experiment in an attempt to see how closely a micro method would check with the macro method. The disappointing results have been published in a previous publication.[1] Since other methods used by the same technician have checked closely it appeared that the variations in the measurements by the micro method were not due to a faulty technician but rather to the method itself, which requires such small quantities of blood and of reagents in general that more than the ordinary technical ability is required in its use. Because of the inconstant results I have abandoned the use of this method.

That our experience with the chances of error with the micro method is not isolated is suggested by the history of a patient who came to us from another state where she had been treated for dia-

[1] Glucose Tolerance and Its Value in Diagnosis, Jour. Met. Res., 1922, **1**, 497.

betes on the basis of a continuous high blood-sugar content. She was on a restricted diet and under insulin treatment. The day after her arrival, no insulin having been given, she showed no hyperglycemia and hyperglycemia did not appear even after a liberal diet. Moreover, the glucose tolerance test showed a normal curve. As it is obvious that severe diabetes cannot disappear in forty-eight hours, I traced the possibility of some error having been made and found that previous sugar estimations had been made by the Epstein method, the findings of which had not been checked by any other method. A repeated examination checked our findings which fortunately for the patient were found to be correct. The clinician is bound to be misled in such an instance if he is not on his guard, and we believe in view of our experience that the glucose tolerance test gives the most dependable evidence.

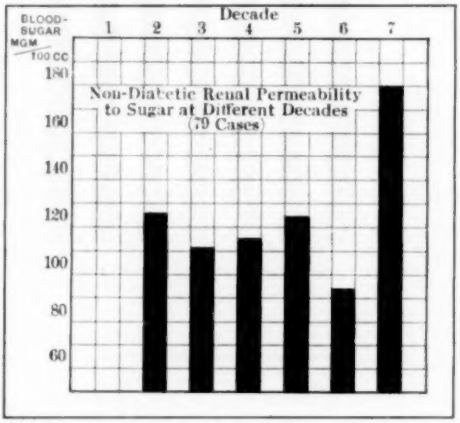

CHART IV

Charts IV and V illustrate graphically the differences in renal permeability at the different decades of life in diabetic and non-diabetic cases. With the exception of the second decade, the rise in the permeability level is slight and fairly constant. I cannot explain the abrupt and decided rise during the second decade except on the basis of the sudden onset of diabetes which is characteristic at this age. Perhaps a high blood-sugar figure accompanies this sudden development of the disease and changes temporarily the kidney permeability level.

Chart VI gives the average diabetic and non-diabetic renal permeability thresholds in 166 cases, showing the markedly higher level found in diabetic patients.

Summary and Conclusion. The finding of glycosuria alone is not a sufficient basis for the diagnosis of diabetes. If glycosuria is innocent then it is due to a low renal threshold or to an overflow of glucose as the result of a very heavy carbohydrate meal. On the other hand, if glycosuria is due to diabetes it is not innocent and there-

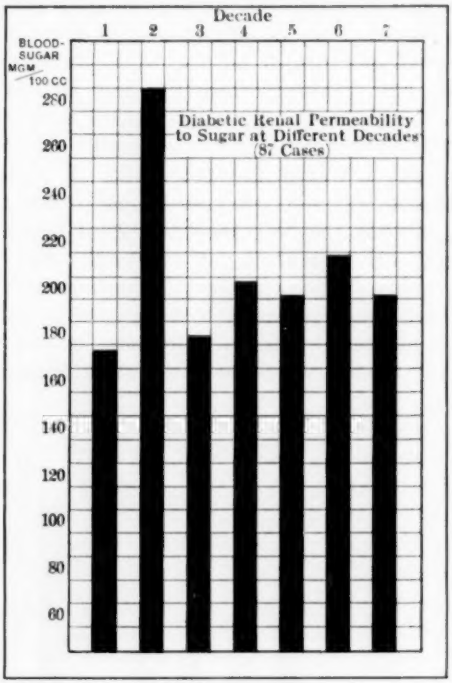

CHART V

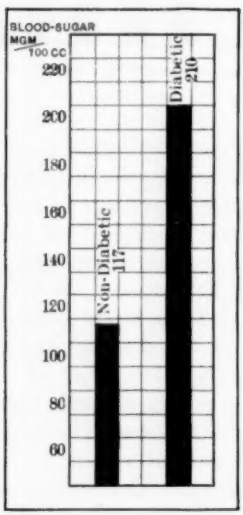

CHART VI.—The average renal permeability level in 166 non-diabetic and diabetic cases.

fore the presence of glycosuria should be considered an indication for the institution of such procedures as will determine its cause in the individual case. All that is required in such a case is to instruct the patient to eat a heavy carbohydrate meal and to present himself at the office *exactly* three hours thereafter for a blood-sugar estimation and urine examination. If the individual is normal, there will be no hyperglycemia because, in a normal individual whose tolerance for carbohydrates is unimpaired, the blood-sugar content will be normal or subnormal. On the other hand if at the end of the three-hour postprandial period the blood sugar is above the normal level, the patient is definitely a diabetic whether or not there be sugar in the urine. Thus, for diagnostic purposes, the three-hour postprandial blood-sugar estimation is of much more importance than the fasting blood-sugar estimation.

The length of time since the last meal should always be considered when blood is taken for a general estimation since the blood-sugar content varies during the day and a postprandial rise may be misinterpreted as a result. In the continued study of a case it is essential that the blood be taken always at the same periods with reference to meals, the test always beginning with a fasting blood-sugar estimation.

As has already been emphasized a fasting blood-sugar estimation alone is not of diagnostic value, since in even a severe case of diabetes the blood sugar content may be normal if the patient is on a proper diet. Due to this very fact some of our own cases have been misinterpreted in other laboratories, where, since the fasting blood sugar was found to be normal and glycosuria not present, the patients were told that they did not have diabetes. As a result these patients returned a few months later in such an advanced stage of diabetes that the administration of insulin was required. As the result of an error of this nature, a comparatively mild case of diabetes may become a severe case.

Microtechnic may lead one astray, and we believe that in general practice the glucose tolerance test gives more dependable and consistent results.

THE RELATION OF TETHELIN TO PITUITRIN.

With a Study of Two Cases of Diabetes Insipidus.

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In 1916 T. Brailsford Robertson reported the isolation of a chemical compound from the extracts of the anterior lobe of the

pituitary gland. This substance, he named Tethelin. He then proceeded to study its effects upon the growth of white mice and to compare the effects obtained with those he had found when he had studied the effects of anterior lobe substance unmodified by chemical treatment. His final conclusion was that "the effects of tethelin upon the growth of white mice resemble in every particular the effects of the administration of the whole anterior lobe." He therefore considered himself justified in regarding tethelin as the active growth-promoting principle of the anterior lobe of the pituitary. Other studies made by Robertson and his co-workers showed that tethelin possessed a growth-promoting property for carcinomata in rats, in hastening tissue regeneration after inanition atrophy and in granulating wounds. In fact, a commerical preparation of tethelin was put upon the market, to be used in the treatment of indolent ulcers and burns. Barney[2] and Mayo[3] reported good results from its use in such cases.

The physical and chemical properties of tethelin were studied by Robertson and by Schmidt and May.[4] Upon the bases of his chemical analyses, Robertson declared that the substance belonged to the group of phospholipins but possessed the singular property for a phospholipins of being soluble in water, as well as in certain mixtures of ether and alcohol. It is also soluble in *boiling absolute alcohol*, as this is the medium which is used in separating it from the whole anterior lobe. It is important to bear this property in mind. Upon hydrolysis it yields inosite, and it contains nitrogen and phosphorus in the ratio of 4 to 1. It can be saponified, with a saponification value of about 87 mg. of KOH per gram and it has a mean iodin absorption value of 33.2 per cent. It can form 5 per cent aqueous solutions, appearing turbid brown at this concentration, but a 1 per cent solution is only slightly opalescent. Its aqueous solution does not give a biuret reaction, nor does it reduce Fehling's solution either before or after hydrolysis with barium hydroxide or with the latter followed by sulphuric acid. Ehrlich's reaction is positive, indicating the presence of an acetylated oxyamino group, and Wiedel's reaction is positive, indicating the probable presence of an iminazolyl radical. We shall return to the question of the significance of this radical for certain physiological effects of tethelin.

The work of E. P. Smith has also thrown light upon the growth-promoting activities of the anterior lobe of the pituitary and upon the physicochemical properties of the active principles. In a series of investigations, curiously enough begun in 1916, and summed up in his monograph on "The Pigmentary, Growth and Endocrine Disturbance Induced in the Anuran Tadpole by the Early Ablation of the Pars Buccalis of the Hypophysis," he showed that by the removal of the anlage of the anterior lobe in the anuran tadpole, a cessation of differentiation as well as growth was produced, but

that this effect could be prevented or controlled by feeding whole anterior lobe. He also showed that the active principle concerned in this effect was *not* soluble in boiling water or *boiling alcohol*. These results of Smith in finding a growth-promoting substance in the anterior lobe which is not soluble in boiling absolute alcohol collide directly with the work of Robertson on the properties of tethelin which is soluble in boiling absolute alcohol. It follows either that the active principles of the anterior lobe of the pituitary in the anuran tadpole is entirely different from that of the white rat, which is highly improbable, for in the case of the feeding experiments of Smith, mammalian material was used, or that there are two different growth-promoting principles in the same lobe, which is also highly improbable. The possibility arises that the growth-affecting properties of tethelin, which are by no means as conspicuous as those observed by Smith using whole anterior lobe in the tadpole, may be the collateral effects of a substance having indeed another function.

This possible function has been suggested by certain physiological effects obtained when tethelin is chemically modified. In 1917, Schmidt and May[1] published a paper on the possible derivation of the active principles of the posterior lobe of the pituitary body from the tethelin produced by the anterior lobe. They based their suggestion upon the fact that tethelin when treated with barium hydroxide yielded a substance exerting on the uterus and on the blood-pressure an action similar to that of posterior pituitary extracts, usually called pituitrin. In view of the untenability of the conception of tethelin as the growth-promoting principle of the anterior lobe, as shown by the solubility findings of Smith, this suggestion remains the only one providing a possible function for tethelin (which is certainly a unique substance obtainable only from the anterior lobe) namely as a precursor of pituitrin.

In 1919, Abel and Kubata[5] isolated from posterior lobe extracts, commonly called pituitrin, the substance B-iminazolylethylamin which they called histamin because of its chemical relation to histidin, an amino-acid which may be found in the hydrolysates of various proteins. They showed that histamin is present in all the tissues of the body, and at first put forward the claim that it is the smooth muscle-contracting substance of posterior lobe extracts. They based their claim upon the fact that histamin causes an uterine reaction similar to that of pituitrin. This observation was first made by Roth and confirmed by Nieulescu. Guggenheim, however, had pointed out a difference in stability of histamin and pituitrin toward alkali in the same year that Roth pointed out the similarity of their action. Dudley,[6] in 1919, confirmed this finding of Guggenheim, demonstrating that upon contact with sodium hydroxide, pituitrin like adrenalin loses its power to cause specific reactions while histamin is not so affected. Also that tryptic

digestion destroyed pituitrin but not histamin, and that definite solubility differences in chloroform and butyl alcohol were marked. In 1920 Hanke and Koessler[7] showed by a colorimetric method that histamin was not present in perfectly fresh beef pituitary. In 1922, Abel and Rouiller published their observations on the preparation of a single specific substance from the infundibulum, which has both oxytocic and vasomotor properties as well as a powerful stimulating effect upon the kidney and estimated that in equal concentrations pituitrin would be found to have fifty times the uterus-contracting power of histamin. Their observations dispose finally of the claim that pituitrin and histamin are identical.

Yet the problem of the relation of tethelin to pituitrin and to histamin remains. As mentioned, the tethelin gives reactions showing presence of an iminazolyl radical, which is also present in histamin. On the other hand hydrolysates of tethelin prepared with barium hydroxide give pituitrin-like oxytocic and vasomotor effects. It has been recognized that the specific test for pituitrin is its ability to reduce diuresis in the disease diabetes insipidus. It occurred to the writer to test the action of barium hydroxide hydrolysates of tethelin upon the blood-pressure and upon the diuresis of two patients with diabetes insipidus whom he had under observation, one a boy of ten and the other a man of forty-five. Both the patients had shown satisfactory response to pituitrin as far as their diuresis and general comfort was concerned.

Case I.—Boy, aged ten years, of Hebraic descent. The father is a blonde, large individual, with a tendency to obesity but active; the mother is dark, obese and undersized. There is no history of familial diseases, but individuals in both paternal and maternal families tend to run to extremes, either large and tall or smaller than the average. The patient, an only child, was born at term and said to weigh 9 pounds at birth. He was in every way a large baby, the mother said. He was kept on the breast until three months of age, but developed vomiting which finally caused transfer to artificial feeding. Much difficulty was encountered in trying various mixtures which he could not assimilate, until one was found at the age of six months upon which he thrived, the teeth appearing at the same time. He gained quickly, perhaps as a result of overfeeding, for he weighed 33 pounds at one year. He did not gain so much during the second year, but kept over the average. At seven he weighed 54 pounds and first went to school, where he was said to be quite bright, particularly in mathematics. At eight, he had scarlet fever severely, and was in bed ten weeks, with reported development of a cardiac lesion which later cleared up. After a few months he began to complain of weakness, headache, trouble in using eyes, and great thirst. Frequent urination, nocturnal and diurnal, with thirst. He drank now about 7 to 8 quarts of water a day and passed about the same.

The physical examination showed a rather emaciated-looking boy, weighing 49 pounds and 3 feet 11 inches tall. He had a pale, sallow complexion. He was found weak, lying in bed and responding to questions reluctantly and feebly. His general build had the striking slenderness and suggestion of bony fragility that reminded one strongly of the somatic type present in the Lorraine variety of pituitary infantilism. The head was long, high and narrow; the hair of the head was light and very fine, that of the eyebrows was so light as to be almost invisible, and the outer half was practically missing. The nose was thin and high-bridged. The interpupillary space was $2\frac{3}{8}$ inches and the eyes had a somewhat mongoloid slant. The ears were oval in shape and there was very slight development of the free lobe. The teeth were large and rather trapezoid in shape and markedly separated. The palate was high and narrow, arched like a Gothic arch. The tonsils were present and just visible. The neck was relatively long in relation to the size of the head and trunk, and the thyroid gland was enlarged. Over it a soft, low systolic bruit could be heard. The heart and lungs were negative, the liver and spleen could not be felt. The hands were oblong in shape, and the lunulæ of the fingernails were all quite marked. There was no leuconychia; no Chvostek sign. The skin was fine, moist and quite light, with a few pigment spots on the neck and forearms. On stroking the skin of the chest gently, broad red lines appeared which lasted some time. The body measurements were: Torso: Lower extremity ratio, $15\frac{1}{2}$ inches to $27\frac{1}{2}$ inches; quotient, 1.8; span, 45 inches; chest circumference, $25\frac{1}{2}$ inches; sitting height, 29 inches. Examination of the blood: Hemoglobin (Sahli modified), 90 per cent; leukocytes, 8600 per c.m.; polymorphonuclears, 42 per cent; lymphocytes, 54 per cent; eosinophiles, 4 per cent. The Wassermann test was negative. Blood sugar, 65 mg. per 100 cc; cholesterol, 155 mg. per 100 cc; CO_2 combining-power of plasma, 55 volumes per cent; calcium, 9.6 mg.; inorganic phosphate, 2.7; chlorides, 760 mg. per 100 cc. Urinalysis showed: Reaction acid; specific gravity, 1001; color like that of distilled water; negative for albumin, sugar acetone and indol. Microscopical examination, negative. Eye examination: Slight bilateral concentric contraction of the visual fields and a marked contraction of the color fields, greatest on the temporal sides. Roentgen-ray examinations: Of the head showed a small completely enclosed sella turcica, while that of the chest showed a large shadow in the mediastinal region, presumably the thymus.

The blood-pressure, taken several times, averaged 95/60. The quantity of urine observed over a period of a week, averaged between 7000 to 8000 cc.

It was then decided to observe the effect of pituitrin upon the blood-pressure and the urinary output. The effect upon the urine was to reduce it to 1800 cc for the following twenty-four hours.

Upon the blood-pressure, the effects were as follows: After fifteen minutes, 100/60; after thirty minutes, 125/80; after 45 minutes, 135/80; after sixty minutes, 145/90; after one hundred and twenty minutes, 130/90; after three hours, 120/80; after 4 hours, 95/60.

There was marked subjective improvement during the twenty-four hours, the color of the face and the general vivacity increasing greatly as well as the appetite. Also a bowel movement occurred without resort to cathartics. On the day after, nothing was given and the quantity of urine rose to 6500 cc. The day after was chosen as the one on which to give the barium hydroxide hydrolysate of tethelin; 1 cc was given hypodermically. There was no effect upon the output of urine. Upon the pressure, the effect was as follows: After fifteen minutes, 100/65; after thirty minutes, 120/70; after forty-five minutes, 130/70; after sixty minutes, 135/85; after one hundred and twenty minutes, 130/70; after three hours, 110/65.

These determinations were repeated upon alternate days, with pituitrin and with tethelin hydrolysate, with the same results. It appeared therefore that while pituitrin had definite effects upon *both* the urinary output and the blood-pressure, the substance produced by the barium hydroxide treatment of tethelin affected only the blood-pressure. It follows that pituitrin is not present in the hydrolysate of tethelin, and that the possibility that tethelin may be the physiological precursor of pituitrin cannot be sustained. This conclusion was confirmed by observations made upon a second patient with diabetes insipidus, an adult who was seen some six months later, the details of which I shall now present. The first patient was kept comfortable with injections of pituitrin given on alternate days, and small doses of whole gland pituitary substance. But he died about a year and a half later of penumonia, following an upper respiratory tract infection.

Case II.—E. R., a rabbi, aged forty-five years, married, with six children, all of whom are living, about a year and a half ago began to urinate large amounts frequently. He is now passing from 10 to 20 quarts daily. At the same time he has put on over 50 pounds in weight. He was born in a small town in Russia. The family history was negative except that an uncle and a grandfather had suffered from diabetes mellitus. The past history showed that he had had scarlet fever at the age of seven and mumps at the age of thirteen. The mumps had apparently not been complicated by orchitis. The intellectual development had begun early, while the sexual development had begun late, hair on the face not appearing until the age of sixteen. He was admitted to the rabbinate at the age of twenty-three and had held the position of rabbi in his community until five years ago when war conditions forced him to emigrate to America. Here he had supported himself by teaching Hebrew, but had never obtained the rabbinate of a synagogue.

There had been much worry over economic considerations. He had married at twenty-five.

About a year and a half ago began to experience abnormal thirst. He found himself drinking every hour, then almost all the time, with a feeling of insatiable thirst. He began to pass large quantities of urine at the same time, frequently, and also began to put on weight. A desire for sweets had always been a personality characteristic; but now this desire for sweets also increased greatly and there were times when he would eat a pound to a pound and a half of chocolate a day. But this had no relation to the thirst or frequent urination, because these would continue on days when he would prevent himself from indulging in sweets.

The physical examination showed a rather large, robust man who outwardly did not appear at all ill. He weighed 187 pounds and was 5 feet 7 inches in height. His span, however, was 5 feet 9 inches. His torso measured 17 inches, while the lower extremity was $36\frac{1}{2}$ inches. His head was rather large for the height, and brachycephalic. The effect of the facial contour was rounded with prominent cheek bones. The interpupillary space was $2\frac{3}{4}$ inches, while the intermalar space was $5\frac{1}{4}$ inches. The nose was short and pointed. The ears were large, with a horizontal upper border, and the lobe running into the face. The chin was covered by a profuse growth of a black beard. The teeth were in very poor condition showing much decay and caries, with several of the molars missing. The upper central incisors were large and separated and showed large areas of erosion. The lateral incisors were small and pointed and showed several chalky white spots. The canines were not pointed. The palate was markedly arched and the tonsils were present, but did not appear diseased. The thyroid was palpable but not enlarged. The heart, lungs and abdomen were negative. The skin was smooth and soft except on the outer part of the fibiæ where it was rather hyperkeratotic. The hair of the scalp was thick, black and gray. The eyebrows were well-developed and there was a nasal brow. The axillary and pubic hairs were well developed, but there was very little hair on the extremities. The general contour of the body showed an excessive deposit of fat in the breast regions, above the pubis and over the hips and thighs and below the nape of the neck giving the body a feminine appearance. The hands were distinctly spade-like in appearance, the fingers were straight and flat, the nails showed a number of white horizontal lines. Neurological examination: Slight positive Chvostek sign. Examination of the blood: Hemoglobin (Sahli modified), 85 per cent; erythrocytes, 4,500,000 per c.mm.; leukocytes, 5600 per c.mm.; polymorphonuclears, 56 per cent; lymphocytes, 42 per cent; eosinophiles, 2 per cent. The Wassermann reaction was negative. The blood sugar was 0.78 mg. per 100 cc; cholesterol, 175 mg. per 100 cc; CO_2 combining-power of the plasma, 50 per cent; calcium, 8.7 mg.;

inorganic phosphate, 3.5 mg.; chlorides, 820 mg. per 100 cc. Urinalysis showed: Reaction acid; specific gravity, 1005; color like that of distilled water; no albumin, sugar, acetone or indol. Microscopically, a few leukocytes and cylindroids. Eye examination: Marked temporal pallor of the discs and irregular contraction of the visual fields, with concentric contraction of the color fields. Roentgen-ray examinations: Showed an enlarged sella turcica with marked erosion of the anterior and posterior clinoids and of the dorsum. That of the chest showed no pathological shadow in the mediastinal region; that of the hands showed complete closure of the epiphyses and rather marked tufting of the terminal phalanges and decreased density of the compact zone of the terminal phalanges and decreased density of the compact zone of the bones. The blood-pressure, taken daily for a week, averaged 110/70. The urine over the same period varied between 8000 and 11,000 cc. The effect of pituitrin upon the blood-pressure and urinary output was then determined. One cubic centimeter was injected intramuscularly.

The effect upon the blood-pressure was as follows:

After fifteen minutes, 115/70; after thirty minutes, 135/85; after forty-five minutes, 145/85; after sixty minutes, 150/90; after one hundred and twenty minutes, 135/80; after three hours, 120/80; after four hours, 110/80. The urinary output for the next twenty-four hours was 2460 cc, and its specific gravity rose from 1006 to 1012. The patient declared that he felt strong enough to get out of bed. His appetite was markedly improved, while the craving for sweets was greatly diminished. On the following day, however, he complained of weakness and the urinary output was 8900 cc. He expressed a continuous desire for sweets. Three days later he was given an injection of the barium hydroxide hydrolysate of tethelin. There was no effect upon the output of urine, which was 9600 cc. Upon the blood-pressure however, there was a definite effect.

After fifteen minutes, 110/70; after thirty minutes, 130/75; after forty-five minutes, 140/80; after sixty minutes, 155/90; after one hundred and twenty minutes, 150/85; after three hours, 130/80; after four hours, 115/85.

Conclusions. It is evident that while the injection of pituitrin in both cases of diabetes insipidus produced a definite effect upon both the blood-pressure and the urinary output, the barium hydroxide hydrolysate of tethelin produced a pressor effect only upon the blood-pressure, but not upon the urinary output. This seems to prove the lack of identity between the active principle present in the solution known as pituitrin and the pressor substance produced from tethelin by barium hydroxide hydrolysate. This would appear to make invalid the hypothesis which has been advanced to explain the presence of tethelin in the anterior lobe of the pituitary gland, namely, that it is produced in that lobe to act as the chemical pre-

cursor of pituitrin, which could then be looked upon as a derivation of tethelin. The pressor reactions obtained after manipulation of tethelin may be due to a freeing of the imino-azolyl radical indicated by Wiedel's reaction. This may also account for statements concerning the presence of histamin in old preparations of pituitary. The function of tethelin, if it is a physiologically occurring substance and not a by-product of the chemical manipulation of the dead glandular material, therefore remains a mystery.

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GASTROINTESTINAL ULCERATION FOLLOWING CUTANEOUS BURNS. WITH REPORT OF CASE.

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Historical. Ulceration of the gastrointestinal tract following external burns is a subject that has attracted attention at intervals ever since 1842. In that year Curling[1] made his report of 12 cases of external burn with subsequent lesions in the intestine. Ulceration was proved at autopsy in nearly all of these cases, by the occurrence of perforation or hemorrhage in 2 or 3 others. In 2 cases inflammation only was found. In all of these cases, the lesions found were in the duodenum within an inch of the pylorus.

Curling's name has been associated ever since with duodenal ulcers subsequent to external burns. Most text-books barely mention the subject: (1) Because of its uncommonness and the lack of precise knowledge and (2) on account of the slight diagnostic and therapeutic interest.

Curling himself rather discounted the earlier observations of Dupuytren on the ground that the inflammation and ulceration described by the latter were not limited to the duodenum. Curling undoubtedly gave the first connected specialized description; but

on the question of priority the reader may formulate his own opinion from the following facts:

Dupuytren[2] in 1832 clearly recorded the finding of gastrointestinal inflammation and ulceration after burns. He does not delimit the areas involved—it is probable that the lesions occurred in various parts of the stomach and intestine. Specifically, he speaks of the whole ileum being bright red; of fluid blood being present in the stomach and in the intestines; of the third case he says: "In the stomach and near the pylorus there are numerous small and nearly miliary ulcerations. The whole ileum is deep red." Curling's reflection on the earlier observations implies that he considered the duodenal localization specific. This is certainly an unjustified assumption; other cases have been described in which the stomach was the site of ulcers; the present paper will record such a case.

MacCallum[3] says, in connection with the subject of burns: "The duodenal ulcers so often mentioned are really rare." The textbook allusions are correspondingly timid; the only real descriptions given are in special articles.

Descriptive. Clinically the occurrence of ulceration may be heralded by hematemesis, melena or the signs of intestinal perforation. These events may take place at any time from four days to several weeks after the external burns have been sustained. One of Dupuytren's patients died in thirty-six hours and ulcers of the stomach were found. Curling's patients that showed definite ulceration at autopsy died from six to twenty-one days after being burned. In one case where the patient died on the fourth day only an inflammatory process was found in the duodenum. Perforation occurred in one case as early as the sixth day.

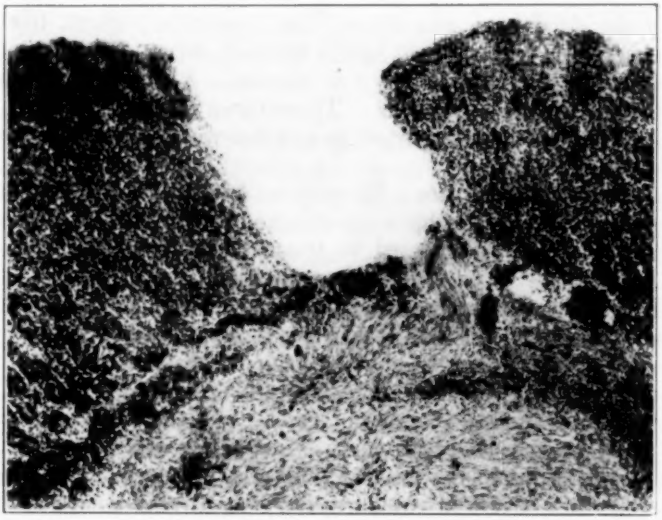
Rokitansky, as quoted by Swain,[4] says that duodenal ulcer may be fatal in from four to sixty days after the burns are received. Simpson[5] describes acute abdominal symptoms, suggestive of intestinal ulceration, coming on with fever more than one hundred days after the occurrence of extensive burns. This patient, however, recovered.

Not all cases of intestinal ulceration after burns have a fatal ending. Curling remarks that death from other causes, some time after burn, occasionally leads to the discovery of recently healed ulcers in the duodenum.

Pathology. The external burns may be of the first degree or more severe; in area that may be very extensive, in some cases they have involved a relatively small part, *i. e.*, less than one-fifth of the body surface.

Accurate description of the ulcers is not usually attempted in the literature. They may be miliary in size, the largest are an inch or more in diameter. A sharp edge and a clean base, perhaps grayish, are usually mentioned. The mucous membrane alone has

been involved in some instances, in others all the coats of the intestine have been penetrated. The depth of the ulceration probably is dependent in part on the factor of time; but this is difficult to determine because the time at which ulceration begins cannot be known. Perforation certainly has occurred by the fourth day after the burning; some ulcers never perforate, but heal. In the cases where perforation takes place as late as the eighteenth or nineteenth day, the ulcerative process may have had its inception the day before or two weeks before. Seldom is ulceration found when death takes place after a longer time than three weeks. It may be said, therefore, that the ulcers develop soon after the burn and progress rapidly to perforation, hemorrhage or healing. They do not become chronic.



Section through a miliary ulcer, showing loss of mucosa, inflammatory reaction in surrounding mucosa, membrana propria and submucosa (lower power).

Dupuytren is well quoted here: "It has been demonstrated by postmortem observation, that when an individual has perished in a general conflagration, in the midst of flames, or a few moments after being rescued from them, inflammation has not had time to develop itself in the intestinal canal, but we there find marks of a violent congestion. If some days have elapsed since the accident, we find, on opening the bodies, all the distinctive marks of gastro-enteritis. Finally, if the patient has died at a still more remote period, we find in the viscera and particularly in the digestive apparatus, profound alterations. The mucous membrane presents more or less vivid red patches and more or less deep ulcerations."

The mucosa adjacent to the ulcer is not grossly changed; but

Leonard,[6] in his case, observed microscopically that the cells near the ulcer were obscured; a layer of polymorphonuclear cells was seen covering the base.

Localization. In all of Curling's cases the ulcerations, when they were seen, were in the duodenum, near the pylorus. He rather implies, by his reference to Dupuytren, that lesions elsewhere in the alimentary canal are of a different nature. It is difficult to understand this assumption if the latter ulcers have been found under similar circumstances. Stengel,[7] after calling attention to the definite relationship between cutaneous burns and duodenal ulceration, says that " in exceptional cases, ulcers in the stomach or the lower part of the intestinal tract have been found associated with such duodenal ulcers." One of Dupuytren's cases showed numerous small and large ulcers in the stomach, near the pylorus, while the duodenum was intact. In Leonard's patient, likewise, 24 small ulcers were present in the stomach, most of them near the pylorus, and the duodenum was normal. A third such case is reported in the present paper. These three instances are the only ones of the kind thus far found in a rather wide search through the literature.

Etiology and Mechanism. Hypotheses as to the cause of death in cases of superficial burn have not attained to the dignity of theories; and so it stands with regard to the causation of gastrointestinal ulceration.

Ulcer is not a constant sequela of burn. Fenwick[8] states that it occurs in 6.2 per cent of all fatal burns. In Erichsen's[9] series of 68 cases, two were known to have had duodenal ulcers.

Bardeen,[10] in his studies of the visceral changes after burns, lists most of the possible theories of causes of death, without giving any of them especial preference. Most of the same theories have been invoked in explanation of the seemingly unaccountable occurrence of these ulcers in the alimentary canal as a complication of burns on the skin. Just as in the case of peptic ulcer and probably for the same reasons, any theory is difficult of proof. The principal hypotheses may be given brief mention.

It is conceivable, say some writers, that the damage to the skin, together with shock, suppresses the cutaneous secretion and that sympathetically the secretion of the intestinal mucosa is inhibited, rendering the tissues vulnerable. Curling states that in one case there were changes in Brunner's glands. This suggestion does not account for the ulcers found in Leonard's case, for instance, where the skin was not injured, but the burn consisted of a baking of the pelvic tissues, after Percy's method for the treatment of carcinoma of the cervix of the uterus.

That in the burned tissue is elaborated a toxic substance is another view. This substance may be excreted into the intestine. As the duodenum is peculiarly the site of the lesions, some color is given

to Hunter's[11] theory that the presumptive toxin is excreted by the liver in the bile. Some experimental work has been done to substantiate this view. Hunter injected toluylenediamin into dogs and noted ulceration of the duodenum. Fenwick after tying the common bile duct failed to produce ulcers in this way. Various attempts to reproduce ulcers by injecting extracts of burnt skin have failed, except that Busse[12] in this way induced hemorrhage and inflammation; these were not limited, however, to the duodenum but occurred also in the jejunum and stomach. Busse is authority for the statement that similar lesions in the duodenum may be found in those who have died of carbon monoxid poisoning.

Catiano[13] concludes that a toxin reaching the intestinal wall causes a reduction in its natural alkalinity, allowing digestion of the mucosa to ensue. Cooke[12] thinks that reflexly the antiferments of the mucous cells are destroyed.

Minute emboli and reflex inhibition of the intestinal circulation are two further suggestions, resting upon no objective support.

Report of Case. A white woman, aged twenty years, was admitted to the Colonial Hospital on January 14, 1924. The story was that the patient's dress caught fire as she passed a gas stove and she was burned on both forearms, both legs from the ankles to the knees, on the left hip and about the left breast. In the past history there was nothing of importance. No gastric trouble had ever been experienced. She had had two children.

Examination showed a woman 5 feet 3 inches tall, weighing 110 pounds. Chest and abdomen negative. The burns were mostly of the second degree. Urinalysis showed a trace of albumin on January 16 and again on January 23; the urine was acid the first time, alkaline the second time. There were no casts, no blood. The burns were dressed with picric acid. The patient was nauseated and vomited frequently; no blood was noted in the vomitus. The urine was abundant at first but began to diminish after January 20. On January 22 she voided only 275 cc and after that very little, involuntarily. Vomiting continued. The patient became irrational. The temperature was elevated on the 17th and thereafter ranged from 99.5° to 103° F., usually above 100° F. No blood was ever noted in the stools. The patient became comatose and died on January 24. The clinical diagnosis was acute uremia due to external burns.

Necropsy. The subject is a young white female, rather emaciated. Numerous large second and third degree burns are present on the arms, body and legs. Rigor mortis is very slight. The peritoneal cavity is dry. The muscles and most of the tissues appear desiccated. The liver is of normal size, light brown in color and of firm consistency. On section the liver substance shows a slightly convex surface, yellowish-brown in color, with the lobular markings distinctly outlined by bloodvessels. There are small areas of yellow

mottling, indicating fatty change. The gall-bladder is normal. The spleen is normal in size and consistency, of a purplish-red color, with no excess of pulp or fibrous tissue. The Malpighian corpuscles are large and prominent. The kidneys are of average size, dark purple, with capsules stripping readily. The renal tissue is a little more bloody than normal, the cortex is about 6 mm. in thickness, with fairly distinct striations. The pyramids and columns are slightly swollen. Throughout the tissue, especially in the inter-pyramidal portions, there is a moderate amount of yellow streaking. Pelves, ureters and bladder are normal.

The stomach is greatly dilated, containing a cloudy liquid. The external surface is closely speckled with light gray areas, 2 or 3 mm. in diameter, which appear more translucent than the other portions. When the stomach is opened these lighter areas are seen to correspond to numerous small punched-out lesions in the mucosa and possibly deeper coats. All of them are within 3 inches of the pylorus. No visible inflammatory reaction is associated with the lesions, which are 40 to 50 in number. The pylorus, duodenum and both large and small intestines, also the appendix, are normal. Nothing abnormal is seen in the pelvic organs. The adrenal medulla is liquescent. The pancreas is large and quite hard, of an orange color. In the lungs there was some congestion and edema of the lower lobes and in the left lower lobe is a small patch of bronchopneumonia. The heart is negative. *Microscopical. Kidneys:* The bloodvessels are moderately engorged. There are a few small extravasations of blood between the tubules. The tubular epithelium is swollen and in many places necrotic. The glomeruli show accumulations of wandering cells. *Liver:* There are patches of necrosis, at the periphery of the lobules. There is a small amount of pigmentation. *Heart Muscle:* Normal except for small hemorrhages between some of the fibers. *Spleen:* Marked engorgement of bloodvessels; large numbers of wandering cells filled with pigment as well as much granular pigment in the tissue. *Adrenals:* Show nothing remarkable; no hypertrophy of the cortical elements. *Lungs:* Moderate edema, patches of bronchopneumonia in stage of red hepatization. *Stomach:* The ulcers do not go deeper than the submucosa. There is a moderate inflammatory reaction in the mucous membrane indicated by numbers of small round cells between the gland elements; these appear most numerous near the ulcers. The bases of the ulcers, however, do not show any layer of leukocytes such as described by Leonard. In a few places the submucosa and the muscularis contain numbers of round cells.

Summary. Ulceration of the gastrointestinal tract is an uncommon complication of extensive cutaneous burns, occuring probably in about 5 per cent of the fatal cases. Inflammation very likely is much more common. The condition was described by Dupuytren ten years before Curling made his well-known report.

The ulcers nearly always are found in the first part of the duodenum; but in a certain number of cases other parts of the alimentary tract are involved. At least three instances are recorded, including the author's case, in which the stomach alone was the site of multiple small ulcers.

The mechanism of the production of these ulcers is shrouded in mystery; but it seems most probable that excretion of toxic material into the gastrointestinal lumen takes place and that the mucous lining is injured thereby; just as lesions of the epithelium of another excretory organ, namely the kidney, are found after burns.

In the present case death supervened on the tenth day after the accident, without any gastrointestinal symptoms having been noted, except vomiting. Multiple small ulcers were found in the stomach near the pylorus, and nowhere else. Acute nephritis was also present.

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REVIEWS.

GRAY'S ANATOMY. Edited By WARREN H. LEWIS, B.S. M.D., Professor of Physiological Anatomy, Johns Hopkins University. Twenty-first edition, thoroughly revised and re-edited. Pp. 1417; 1283 illustrations. Philadelphia and New York: Lea & Febiger, 1924.

THE twenty-first edition of Gray's Anatomy brings up to date one of the most remarkable text-books that has ever been published in the English language. The first edition of this work appeared in 1858 and succeeding editions have appeared from time to time, so that the work has been kept up to date most consistently and most thoroughly. During the sixty-six years that have elapsed since the appearance of the first edition this book has been used by countless generations of medical students. The reviewer knows of no book that can look back to such a long and honored career. Such a past speaks well for the genius of Gray and for the succeeding authorities who have revised the subsequent editions. The new edition follows very closely the original plan of Gray, which on the whole has not been changed in any fundamental respect. In the present edition there have been incorporated new illustrations and some of the older ones have been replaced by new figures. In addition to that, the section on the heart musculature has been added and new material added to the section on embryology of the ductless glands. There are a comparatively few other changes and the new edition remains much as the previous ones. May this wonderful text-book have as wonderful a future as it has had a distinguished past. M.

INTERNAL MEDICINE FOR NURSES. By CLIFFORD BAILEY FARR, M.D., Director of Laboratories, Pennsylvania Hospital, Department for Mental and Nervous Diseases; formerly Associate in Medicine, University of Pennsylvania. Fourth edition. Pp. 377; 75 illustrations. Philadelphia: Lea & Febiger, 1924.

THIS is one of the clearest, most succinct and well arranged text-books for the instruction of nurses that we know of. We have used it for some years now in the classes that are given in one of the large hospitals and it has always been found satisfactory for every need.

It is sufficiently wide in scope to give the nurses a clear idea of medicine, yet it is not so deep and involved that they become quasi medical students rather than nurses. This new edition maintains the high level of the previous editions. M.

A TEXTBOOK OF BIOLOGY. For Students in General, Medical and Technical Courses. By WILLIAM MARTIN SMALLWOOD, PH.D. (HARVARD), Professor of Comparative Anatomy in the Liberal Arts College of Syracuse University. Fifth Edition. Pp. 393; 249 engravings and 3 plates in color. Philadelphia and New York: Lea & Febiger, 1924.

WHILE it is obviously impossible to touch more than the very highest spots of biology in less than 400 small pages, nevertheless this book is far from a mere handbook for high-school students. It should broaden the horizon of students of medicine, as well as of natural history, and form pleasant, instructive reading to the graduates in these fields who still realize that they are students also. In the first seven chapters the principal fields of biology—the various systems of the animal body, cells, tissues, embryology—are illustrated by a single complex animal, the frog. The second and third parts deal with plant and lower animal forms, while the fourth discusses such biological problems as evolution, genetics and adaptation. K.

PATHOGENIC MICROÖRGANISMS. By WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College and Director of the Bureau of Laboratories, of the Department of Health, New York City; ANNA WESSELS WILLIAMS, M.D., Assistant Director of the Bureau of Laboratories of the Department of Health and CHARLES KRUMWIEDE, M.D., Assistant Director of the Bureau of Laboratories; Associate Professor of Bacteriology and Hygiene in the University and Bellevue Hospital Medical College, New York City. Eighth Edition, Pp. 811; 211 engravings with 9 full page plates. Philadelphia and New York: Lea & Febiger, 1924.

FOR a new edition of such a well-known book, little more is necessary than to note the changes from the last edition, which are, however, considerable. The grouping and terminology of organisms conforms more closely to the recent adoptions of the Society of American Bacteriologists. The sections on immunity have been amplified and the authors' experiences in diphtheria immunization

given. Latest information on the value of certain sera and vaccines has been included, together with the new facts about measles, tularemia, scarlet, typhus and Rocky Mountain fever. The chapters on anaërobes, pyogenic cocci, paratyphoid and dysentery bacilli and the higher bacteria are practically rewritten. A forty-three-inch table summarizes details of the commoner bacteria, but repels by its size and clumsiness: Certainly it would not stand much use in its present position. One cannot but regret the careless proof-reading which permits "Promazek," "Leishmannia," "Madsoun," "Tarbardillo," "De Kanif" and "Ocutt" (page 177) and so forth. Nor could I find any reference to the organism of inguinal granuloma, or to the part played by the reticulo-endothelial system in the development of immunity. K.

EPIDEMIC ENCEPHALITIS. By ARTHUR J. HALL, M.A., M.D., CAMB., F.R.C.P., LONDON, Professor of Medicine, University of Sheffield. Pp. 279; 17 plates and other illustrations. New York: William Wood & Co., 1924.

THIS book is made up for the greater part of Lumleian lectures delivered before the Royal College of Physicians of London in 1923. The book gives in great detail all the facts about epidemic encephalitis from the history of the disease to the treatment. The book goes into the subject with great thoroughness and the plates illustrating the pathology and certain stages of the disease are well done.

One of the most valuable parts of the book is the bibliography which makes up eighty-four pages and is composed of two thousand and fifty-six references. W.

INFANTILE PARALYSIS IN VERMONT, 1894–1922. A Memorial to CHARLES S. CAVERLY, M.D., Burlington, Vermont: State Department of Public Health, 1924.

THE Vermont State Department of Public Health has brought together in this volume not only the studies that were made in the poliomyelitis epidemics of 1914–15 but also the earlier contributions of Dr. Charles S. Caverly who was the first to report upon an epidemic of poliomyelitis (1894) in Vermont, in which State epidemics have occurred at intervals since this time.

The epidemic of 1914 was extensively studied by Dr. Lovett, Dr. Aycock, Dr. Amos, Dr. Taylor and others under the supervision of Dr. Simon Flexner. This work was made possible by the contributions of the Rockefeller Foundation. The material in

the present volume has appeared in part in current literature. It represents the application of research from a laboratory standpoint, utilized in a state-wide plan which was adopted for the prevention and treatment of these cases of poliomyelitis, a plan so thorough and comprehensive that it is now very generally adopted and used throughout the country. This volume is a splendid example of what can be accomplished in the study of disease by the coöperation of numerous specialists. It represents the most complete studies of poliomyelitis and the broadest that have ever been carried out in an epidemic. The work will well repay the trouble and expense that the Vermont State Board of Health has gone to in collecting and bringing together this material in order to make it available in a form suitable to the practitioner of medicine and the public health official.

M.

THE ANATOMY OF THE NERVOUS SYSTEM. By STEPHEN W. RANSON, M.D., PH.D., Professor of Anatomy in Northwestern University Medical School Chicago. Second Edition, pp. 421; 284 illustrations, some of them in colors. Philadelphia and London: W. B. Saunders Company.

THE second edition continues to be the most practical short anatomy of the nervous system in English. Special stress is laid on the "developmental and functional significance of structure." The outstanding omission of the first volume has been filled in by a description of the blood supply. One of the best chapters is the general consideration of the cranial nerves and their nuclei from functional standpoint. The chapter on clinical cases illustrating the anatomic principles is new and adds to the book. With but few additions the book is practically the same as the first edition.

W.

THE DIAGNOSIS OF NERVOUS DISEASES. By PURVES STEWART, K.C.M.G., C.B., M.D., EDIN., F.R.C.P., Sixth Edition. Pp. 648; 285 illustrations. New York: E. B. Treat & Co., London: Edward Arnold & Co., Printed in England, 1924.

PREVIOUS editions of this well-known work have been reviewed in this Journal. Stewart in his preface to this edition says that he has never claimed his work to be a text-book of Nervous Diseases but that it is rather an appendix approaching the subject from the clinical point of view and intended to be used in conjunction with other standard works. The reviewer can only state that he would much

rather have this book for reference in neurologic matters than the vast majority of books which pretend to be text-books of nervous diseases.

Instead of discussing the various diseases in the ordinary way, the book is divided into chapters which take up for example—coma, fits and other convulsive phenomena, affections of the cranial nerves, abnormalities of sensation, reflexes, psychoneuroses, cerebrospinal fluid and other phases of neurologic conditions. To the neurologist this book is indispensable and to the general diagnostician it should be an absolute necessity for a quick and comprehensive exposition of nervous disorders. W.

ESSENTIALS OF PRESCRIPTION WRITING. By CARY EGGLESTON, M.D., Assistant Professor of Pharmacology, Cornell University Medical School. Third Edition, revised. Pp. 146. Philadelphia: W. B. Saunders Company, 1924.

THIS little book, pocket size, is packed with facts relative to the art of prescription writing. It should be a very valuable book to lie on the doctor's office desk for immediate reference. M.

A MANUAL OF DISEASES OF THE NOSE, THROAT, AND EAR. By E. B. GLEASON, M.D., LL.D., Professor of Otology, Medico-Chirurgical College Graduate School, University of Pennsylvania. Fifth Edition, thoroughly revised. Pp. 660; 212 illustrations. Philadelphia: W. B. Saunders Company, 1924.

DOCTOR GLEASON'S book is one of the standard text-books in his specialty and as such has run through repeated editions since its first appearance in 1907. The present edition well maintains the standard set by the previous ones and is in every way most commendable. M.

GESCHICHTE DER MEDIZIN. By PAUL DIEPGEN, M.D., PH.D., Professor of Medicine at Freiburg i.B. Pp. 146; 1 illustration. Berlin and Leipzig: Walter de Gruyter and Company, 1924.

THIS, the fourth volume of the History of Medicine Series, deals with the fundamental medical and biologic sciences, from the time of the founding of cellular pathology to the present. It upholds the high standard set by the preceding volumes in the rather surprising amount of information presented in a very brief space, and withal accurately. The work is a part of the "Goeschen Collection" which plans to present in a large series of similar small handy volumes what amounts to a synopsis of human scientific knowledge. K.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Pulmonary Infection with the Spirochætæ and Fusiform Bacilli of Vincent.—McNeill (*Bull. Johns Hopkins Hosp.*, 1924, **35**, 368) reports a unique case of advanced pulmonary disease, involving the upper third of each lung. On physical examination of the emaciated patient there was dulness anteriorly and posteriorly and intensification of the spoken and whispered voice over the upper lobes, and a few moist rales at the apices after coughing. Roentgen-ray examination of the chest showed soft, spotty infiltration in the upper two-thirds of both lungs. There was a leukocytosis of 18,500, with 39 per cent polymorphonuclear eosinophiles. The sputum was mucopurulent, sometimes blood-tinged and abundant. No tubercle bacilli were demonstrable. When the sputum was examined several hours after collection many varieties of bacteria were found, but no spirochætæ or fusiform bacilli. When the sputum was examined one to two hours after collection a few spirochætæ but no fusiform bacilli were seen. However, examination of the sputum immediately after it was coughed up showed large numbers of spirochætæ and fusiform bacilli, identical morphologically with those seen in Vincent's angina. Following four intravenous injections of neoarsphenamin and 100 gr. of potassium iodid daily by mouth, the patient recovered and gained 32 pounds in weight. Roentgen-ray examination of the lungs showed no infiltrate and the physical findings were normal. Nearly three months after treatment was begun there were 11,200 leukocytes with 17 per cent of eosinophiles. A few cases of bronchitis due to these organisms have been reported, and they have also been noted in cases of pulmonary gangrene and abscess. This, however, is the first reported case of pulmonary infection. The author suggests that cases of supposed

pulmonary tuberculosis, in whose sputa tubercle bacilli are not found, may be instances of this infection. The clinical history of this patient was that usually obtained in pulmonary tuberculosis.

Amœbic Bronchitis and the Frequent Presence of Live Entamœbæ in the Sputum and Urine during Acute Amœbic Dysentery.—PETZETAKIS (*Jour. Trop. Med. and Hyg.*, 1924, **27**, 74) describes cases of bronchitis alone or associated with amœbic dysentery characterized by the following symptoms: Expectoration, at times bloody; headache; slight fever; vague thoracic pains, etc. He has studied 10 such cases in which no evidence of amœbic dysentery was obtained. Sputum, macroscopically, was at times glairy, again mucopurulent and sometimes streaked red with blood, resembling that of pulmonary tuberculosis and spirochetal bronchitis. Microscopically, entamœbæ, at times actively motile and filled with red blood cells, were found. They measured 15 to 35 microns. In a study of 34 cases of amœbic dysentery, the details of which have not yet been published, the author found living amœbæ in the sputum alone in 2 cases, in the urine alone in 1 and in both urine and sputum in 3 cases. Morphologically, they were identical with those seen in feces.

A Case of Urinary Amœbiasis.—WORSLEY and BATEMAN (*Jour. Trop. Med. and Hyg.*, 1924, **27**, 278) report their study of a patient with symptoms suggesting renal calculus. Roentgen-ray examination was negative for stone. Urinary examination showed the presence of a few red cells and leukocytes and the precystic stage of Entamœba histolytica. The same microörganism was found in the feces. Treatment with emetine bismuth iodid, 3 gr. by mouth, and emetine hydrochloride, ½ gr. hypodermically, was given daily for five days. This was discontinued. Then for the following six days the patient was given emetine hydrochlorid, 1 gr. hypodermically, daily. The symptoms were relieved, and examination of the urine one month later showed it to be normal.

SURGERY

UNDER THE CHARGE OF

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Fractures of the Shaft of the Femur.—CAMPBELL and SPEED (*Surg., Gynec. and Obst.*, 1924, **39**, 642) say that fractures of the shaft of the femur in children properly treated give excellent results. Callus in children is usually exuberant and non-union even in the presence of

infection or malposition is very rare. Young growing bones have the ability to correct even marked deformities. Immediate reduction and plaster cast is the ideal method of reduction in children, on account of the uniformly good results, the ease of handling and caring for the patients and the certainty that lack of coöperation on the part of the child cannot displace the fragments as often happens with the traction treatment. Simple fractures should be reduced immediately after injury. Early mobilization of joints and massage of soft tissues is of great importance in all fractures, but satisfactory reduction and union should not be endangered by too great enthusiasm in this respect. Compound fractures of the femur will heal without infection in 50 per cent of the cases. Non-union is due chiefly to malposition. Open reductions are rarely indicated in acute fractures of the femur. Autogenous bone grafts are the best method of internal fixation in connection with open reduction. Internal fixation is rarely indicated in children, even in non-unions. It is indicated in malunions in adults where reduction is difficult to maintain. It is always indicated in non-union in adults.

The Mechanism of Postoperative Hemorrhage.—Wilensky and Samuels (*Ann. Surg.*, 1924, **90**, 652) believe that the evidence appears strong that infection is the most important single factor, if it be not the only factor, causing secondary hemorrhage in operative and other wounds. The reported studies show that the presence of drainage apparatus causes an apparently protective thickening of the wall of the vessel, with which the drainage material is in close contact. Infective processes with resultant cell necrosis begins in the intima and spreads to the media. A rupture occurs in the intima and media with the formation of an aneurysmal sac; bleeding follows as a result of the rupture of the aneurysm. It seems that in cases of secondary hemorrhage that the important causative factors include an initial trauma of some kind, plus pressure of the tube or other drainage apparatus in an infected environment.

Exophthalmic Goiter Treated with Insulin.—Lawrence (*Brit. Med. Jour.*, 1924, **2**, 753) state that four severe cases of Graves' disease with hyperthyroidism were treated with large doses of insulin, 60 to 100 units a day. The insulin was well borne and caused no inconvenience. Two of the cases were greatly improved, one being practically normal on discharge from hospital. In both the disease was uncomplicated and of less than a year's duration in women under thirty. It seems unlikely that their improvement was spontaneous or caused by any factor other than insulin. The two others were not essentially benefited, although one gained much in weight and felt better. They were cases of toxic adenoma of the thyroid, rather than of simple Graves' disease, occurring in women of about fifty and of over a year's duration. The idea of treating hyperthyroidism with insulin was founded on the hypothesis of an antagonism between hormones of the thyroid and the pancreas.

Cerebroventricular Study.—Surft (*Northwestern Med.*, 1924, **23**, 452) states that cerebroventricular studies must be used in intracranial lesions to avoid mistakes in diagnosis. Choke disks mean general cerebral edema, or local obstruction to ophthalmic venous outflow either local or general. Spinal-fluid pressure estimations are essential to the study and have no direct relation to the ocular findings, except through the medium of cerebrospinal fluid. The amount of cerebrospinal fluid is shown by the size of the ventricles as depicted by the air in the ventriculogram. Inflammatory lesions increase the amount without necessarily obstructing the circulation of the cerebrospinal fluid, but probably by retarding the absorption. Tumors change the size and shape of the ventricles by pressure, physical displacement or occlusion of the outlet of the fluid, but do not increase the amount except by prevention of the normal circulation of the cerebrospinal fluid. Tumors increase the intracranial pressure only when by their size and position they obstruct the venous outflow of the cranium. The reaction to this pressure is first venous obstruction, then cerebral edema followed by choked disks and lastly increased spinal-fluid pressure, by actual displacement of the ventricular and cisternal fluid. Decompression relieves the venous pressure and then the ocular edema.

Experiences in the Permanency of Radiological Cure in Cancer.—Forssell (*Am. Jour. Roentgenol.*, 1924, **12**, 301) says that his material originates from a small special hospital, of thirty-two beds, in Stockholm. The greatest strength in the system of after-examination lies in the fact that the Swedish Government pays the traveling expenses of poor patients to and from the hospital. Three groups of malignant growths have been observed long enough in large enough numbers to be valuable—cancer of the skin of the face, cancer of the lips and cancer of the uterine cervix. Majority of cases were treated with radium, while only a few cases have had roentgen-rays in addition. Roentgen-rays were employed in cases of large tumors, in treatment of glandular metastases and in postoperative treatment, as well as in deeply situated tumors. In cancer of lower lip the author observed cure lasting from five to thirteen years in 84 per cent of the cases; of 156 cases of skin cancer (superficial) recurrence has been noted in 12 per cent of cases. In infiltrative types recurrence has been observed in 33 per cent of cases. The author discusses the possibilities by repeated radium treatment of the radium recurrences. In the author's opinion radiotherapy in favorable cases, by weakening the tumor gives the normal mechanism of cure a chance of overcoming the disease.

Fibroma of the Abdominal Wall.—Stewart and Moaat (*Brit. Jour. Surg.*, 1924, **12**, 355) say that fibroma of the abdominal wall is a simple fibrous tissue tumor, arising in the musculo-aponeurotic structures of the anterior abdominal wall, especially below the level of the umbilicus and tending to infiltrate the muscle in which it lies. It is met with in women who have borne children to the extent of 80 per cent of the reported cases, and it occasionally occurs in the scars of old hernial and other abdominal operation wounds. In other cases there is a history of local injury. A traumatic theory of origin seems reasonable and the

physiological trauma of labor would appear to be of special importance. These growths are slow in growth in the earlier stages, but with the advent of mucoid or myxomatous change a rapid increase in size may occur. They do not undergo metastasis nor do they endanger life, but there is no evidence that they disappear spontaneously. Treatment should be early and complete removal, with resection of a margin of healthy tissue wherever muscle, fascia or peritoneum is invaded by or is adherent to the growth. Recurrence means incomplete resection and demands a more radical operation. There is no evidence that sarcomatous metamorphosis ever occurs.

Recent Advances in the Diagnosis and Treatment of Urinary Lithiasis.—CUMING (*Jour. Urol.*, 1924, **12**, 383) noted that the evolution of diagnosis and treatment has shown the increased possibilities of nonoperative and of impacted ureteral stone. Nearly all recently impacted stones can be removed cystoscopically. There is definite opportunity to reëstablish healthy activity of the kidneys in the presence of huge unilateral or bilateral stone, with advancing infection. Certain disadvantages are cited for pyelolithotomy which is usually preferable to nephrolithotomy. Necessity is shown for early radical treatment of anuria or intrarenal retention due to stones together with the wisdom of prolonged conservative treatment where adequate drainage persists. Renal and ureteral colic is due to distention rather than mechanical irritation of calculi and is coincident with advancing infection and renal destruction. Silent calculi frequently present the gravest clinical problems and the fewest symptoms attend the inoperable case. Pelvic drainage and lavage is of great value in bilateral stone cases, whether inoperable or prior to operation and in the postoperative case. Ureteral calculi often cause more damage to the kidney than renal calculi. Often nephrectomy is necessary as the result of an impacted lower ureteral calculus.

Early Recognition of Gastric and Duodenal Ulcer by Roentgen-ray Examination of Spontaneous Pneumoperitoneum.—VAUGHAN and BRAMS (*Surg., Gynec. and Obst.*, 1924, **39**, 610) say that free gas in peritoneal cavity was found on roentgen-ray examination in 13 of 15 cases of anatomically proved acute perforation of gastric or duodenal ulcer, and is rarely seen in any other condition, which can be confused with perforated peptic ulcer. Free gas has been seen as early as two hours after the acute perforation occurs. The presence of free air in the peritoneal cavity is demonstrated by observing a clear distinctly bright zone, which shifts on change of posture of the patient. The gas bubble seeks the uppermost portion of the abdominal cavity. The sign is of great value because it makes possible an early and definite diagnosis. Other signs and symptoms should be used in determining a diagnosis. Earlier operation is made possible by this added method of examination. The earlier recognition and prompt surgical treatment will lower the mortality rate of acute perforation of gastric and duodenal ulcer.

PEDIATRICS

UNDER THE CHARGE OF

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Certain Aspects of Enuresis.—AMBERG (*Jour. Am. Med. Assn.*, 1924, **83**, 1300) states that of the various drugs that have been employed in the treatment of enuresis atropin has perhaps held its place best. In experiments on cats it diminished the degree of contraction. In some cases atropin was administered subcutaneously. With one exception, some twenty minutes after the injection and lasting roughly for about fifteen minutes, the pulse-rate diminished. The children became more quiet. Sometimes the atropin exercises a certain influence on the bladder by decreasing the intensity of the contractions, and by diminishing the frequency. This influence is by no means marked. In one case the influence was very marked, yet the frequency of contractions was not diminished, but it was increased and there seemed to be a rhythm present but the contractions were not high. With each contraction there was a desire for urination, and it is very doubtful whether this desire was of lesser intensity. The effect of all medical measures, including drugs, hydrotherapeutic measures, electric treatment and epidural injections, has been ascribed to suggestion. Suggestion may play a part, but the author states that it is not the sole reason for success. It is difficult sometimes to differentiate training from suggestion. Hypnosis sometimes helps. The author has constructed a convenient portable electric apparatus, which is actuated by the wetting, but the current is immediately cut off. This avoids the danger of burning which is present in similar other apparatus.

Signs of Early Rickets.—MOORE (*Jour. Am. Med. Assn.*, 1924, **83**, 1469) made a study of this condition because of the frequency that it was encountered in mild form in the Pacific Northwest. His observations were directed toward finding the signs and symptoms that would lead to earliest recognition. He found that the head and chest furnished the first skeletal evidence of the disease. Craniotabes was demonstrated in 60 per cent of the winter babies. The existence of this condition was most easily determined at the mastoid fontanel. Among abnormalities of the chest indicating rickets are the square, triangular and oval forms as measured at the plane of the fifth costochondral junction. Costomalacia, or softening of the sternal ends of the ribs, appears during the first four months of life and is an important clinical sign. Both genu valgum and genu varum are always preceded by abnormal lateral motility of the knee-joint, which is often the first sign of leg rickets. Knee motility can be measured approximately by hand or accurately by means of a very simple apparatus. Determining the amount of motility has proved valuable for both diagnosis and for prognosis.

Clinic for Treatment of Rickets with Mercury Vapor Quartz Lamp.—WYMAN and WEYMULLER (*Jour. Am. Med. Assn.*, 1924, **83**, 1479) found that rickets was a very prevalent nutritional disorder in Boston. They feel that in such localities special clinics for the treatment of rickets should be organized. Acute rickets can be cured in an out-patient department by ultraviolet irradiation, the treatments being given three times a week, without any other antirachitic medication. Ultraviolet irradiation in combination with cod-liver oil is useful in treatment of acute rickets, and probably hastens the healing processes more than either ultraviolet rays or cod-liver oil alone. Ultraviolet irradiations three times a week prevents the development of rickets. If the progress of manufacturing fused quartz continues it may soon be possible to have quartz windows in every nursery, so that the baby can have its daily sun bath in a warm room. It may also be possible to devise an electric quartz bulb, simple to operate, harmless and inexpensive, which will give off sufficient actinic rays, with from one-half to one hour exposure a day to prevent rickets from developing. A simple lamp of this sort would be a part of the equipment of every nursery, and a daily sun bath with the lamp, when the baby could not be exposed to direct sunlight, would prevent rickets. The authors emphasize that while failure of calcium deposition in the epiphyses is an early and relatively pathognomonic sign of rickets, the fact should not be lost sight of that this failure of calcium deposition is only one of the many manifestations of the disease.

The Diagnosis of Dilatation of the Bronchi in Children by Means of the Injection of Iodinized Oil.—ARMAND-DE LILLE and GELSTON (*Am. Jour. Dis. Child.*, 1924, **28**, 527) describe the technic of this procedure. They found that utterly aside from any other consideration the shadow given in the roentgenogram is of great interest. The contrast between other roentgenographical reproductions and those obtained by means of the injection of iodinized oil offers extremely valuable information, and should permit of definite conclusions. If there is the picture of multiple shadows in the neighborhood of the hilum, with an excessive bronchial ramification, the shadows being joined to the bronchi by a pedicle, the diagnosis of bronchial dilatation is justified. It may be demonstrated later that this conclusion must be modified in the cases of glandular cavities, but until now no such cases have been encountered. If the shadows are confluent, but can be separated by careful examination, the diagnosis of dilatation of the bronchus is again established. If the larger bronchial ramifications, without showing bunched localized shadows, appear noticeably enlarged one must admit a cylindrical dilatation of the bronchus. If there is present a number of shadows along the smaller bronchial ramifications, when they are compared to the normal picture, the diagnosis of a moderate degree of bronchiectasis is warranted. The authors claim that tuberculous cavities may be disregarded, as they are easily enough diagnosed by means of ordinary roentgenograms. It must be noted that cavities left by pulmonary abscesses are usually located far from the hilum and mediastinum, above the diaphragm, and are usually single. Aside from the great diagnostic interest presented by this method of intratracheal injections of iodinized oil in children, emphasis should be

placed on the fact that it is entirely innocuous and further holds out the hope of perhaps having a therapeutic effect of some considerable value. They have observed in a number of young patients a marked lessening of physical signs, indicating a diminution in the size of the bronchial cavities. It would appear that there was a local effect of the iodin. This has not been checked by second injections.

Non-rachitic Softening of the Ribs in Infants and Children.—Hess (*Am. Jour. Dis. Child.*, 1924, **28**, 568) remarks that, although the usual phenomena of rickets are cured by the use of cod-liver oil or ultraviolet irradiations or both, these two procedures have no effect upon the softening of the ribs. Seasonal variation, which plays so important a part in the development and cure of rickets, was found to have no relation to the appearance or recession of this sign, no improvement at all taking place in the summer months. This condition is not amenable to treatment. A striking feature is that the softening was found almost always in infants who were or had been poorly nourished. This was not a characteristic of rickets. As is well known, rickets is frequently met with in babies who are overweight or robust. In this type of baby rickets is not associated with softening of the ribs. No association has been noted between this clinical condition and any particular sign of rickets. It was not associated more often with craniotabes than with beading of the ribs or enlarged epiphyses. The only peculiarity was that the circumference of the heads of many of these infants was large in comparison to that of their chests. This tended to give them a slightly rachitic appearance. Some infants seemed to have a slight hydrocephalus accompanied by a widening of the fontanel. The softening of the ribs and their cartilages led to a sinking of the anterior wall of the chest and to a flattening of the chest. This change in conformation was apparent in some instances on casual examination and was confirmed by measurements of the thorax. Although the circumference of the chest was normal in infants with soft ribs, the anteroposterior diameter was less in comparison to the lateral diameter than in infants with firm ribs. Some of the children had deformity of the chest, commonly called "chicken-breast," or a "funnel-shaped chest." These deformities may result from rickets, but they may likewise come about from other causes. Pneumonia may lead to "chicken-breast." The most common etiological factor of these two malformations is rickets combined with softness of the ribs.

Correlation of Clinical, Roentgenological and Serological Evidence of Rickets in the Breast-fed.—DeBuys and von Meysenbug (*Jour. Am. Med. Assn.*, 1924, **83**, 1563) studied sixty-eight infants, with an analysis of clinical findings, roentgenological picture and blood chemistry. They found that the positive roentgenographical findings, the positive clinical manifestations and the abnormal blood chemistry ran parallel. A few cases in which there was marked disagreement between positive clinical findings and negative blood findings were attributed to residual rickets after the use of cod-liver oil. Epiphyseal enlargement is remarked upon as the most dependable clinical manifestation of rickets. Costal beading appears to be the next most important sign. Although craniotabes occurs regularly in those cases with a low calcium-

phosphate product, it also appears so often and in such a marked degree in cases with normal blood and roentgen-ray findings that it is unreliable if considered alone. This symptom is unreliable because of its appearance at an early age and because of its short duration. Cranial bosses, flaring ribs and bowed legs must be regarded as later changes of rickets. In the first twelve weeks of life the blood does not show any changes that are indicative of rickets. From the twelfth to the twentieth week the blood changes are more pronounced, and after this period there is a gradual return to normal. The seasonal variation of blood phosphates was noted, the lowest ebb being in March.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Acute Ulceration of the Vulva.—McDonagh (*Brit. Jour. Dermatol.*, 1924, **36**, 285) discusses the characteristics and differential diagnosis of ulcerations of the vulva due to Doederlein's bacillus (*Bacillus crassus*) and Vincent's organism. The two conditions have many points in common. In both, the local process is ushered in by constitutional disturbance, chills and fever. In neither disease is the lesion autoinoculable, or transmissible to animals. Aphthous ulcers in the mouth coincidently with vulvar ulceration in one of his cases lead the author to question whether, from the finding of both organisms in the mouth lesions, there may not be a relation between the Doederlein organism and the Vincent fusiform bacillus. The author, widely known for his heretical views on the etiology of syphilis, proposes for consideration the fundamental relation of the two vulvar conditions named and cites as analogous examples the conditions known clinically as granuloma pudendi and ulcus molle serpiginosum, in which, McDonagh believes the Ducrey streptobacillus takes on an intracellular habitat and a capsular form. In discussing ulcus acutum vulvæ, McDonagh emphasizes the youth and frequent virginal condition of the patients; the severity of the pain, which may even cause retention of urine; the grayish-white surface of the ulcers; their localization on the inner aspects of the lesser labia; the fact that no erosion precedes the ulcer; the lack of tissue destruction as compared with Vincent's infection of the same region, and the absence of a distinctive foul odor, as important descriptive and differential points as against Vincent's ulceration. The Doederlein bacillus is Gram-positive, varies much in length but is of uniform thickness (0.5μ) and has right-angled ends. The bacilli are frequently found in short chains, and long forms may stain unevenly. Culture is possible on maltose ascitic-fluid agar, preferably under anaërobic conditions. Vincent's organism may cause an infection

de novo or a superinfection. Inguinal adenitis is common. The odor is most characteristic and highly offensive. Erosions appear first, followed by ulceration and incredibly rapid phagadenic destruction of tissue. Bathing with hydrogen peroxide and the administration of 2 or 3 injections of arsphenamin and no more, is recommended. The author states that if this number of injections is exceeded, the process may light up again and extend with renewed violence. The author believes that syphilitic patients are specially prone to develop Vincent infections.

Pigmentation of the Skin Associated with Lymphosarcoma.—The report of WARTHIN, CRANE and JACKSON (*Arch. Dermat. and Syph.*, 1924, **10**, 139) is of interest to the dermatologist because of a discussion of the interrelations of the various pigmentary syndromes associated with abdominal pathology and endocrine involvement. Speaking of acanthosis nigricans, the pigmentary and papillary dystrophy of the skin associated in adults with malignant processes, in the abdomen and sometimes seen in juveniles without a malignant background, the authors emphasize the variety of clinical pictures included in the designation. Emphasis should be placed in these cases and in true Addison's disease upon atrophy of the chromaffin tissue as the etiologic background of the pigmentation. Warthin and his co-workers advance the view that pigmentation of the skin in these abdominal sympathetic syndromes is the result of the activity of reticuloendothelial cells lying in or near the walls of the capillaries of the corium, rather than of the activity of the basal layer of the epidermis. The source of cutaneous pigmentation is then, the chromatophore in the cutis, not the melanoblast in the epidermis. In the cases reported, a pigmentation of the surfaces of the lymph nodes nearest the skin leads the authors to infer that an actinic source such as roentgen-rays or light is responsible for the formation of melanin. To quote their statement "We may advance the hypothesis that, as the result of atrophy or destruction of chromaffinic tissue in the abdominal sympathetic ganglions and suprarenals, there is a disturbance in the production of the aromatic compounds of the pyrocatechin group (mother substances or precursors of suprarenalin) which, circulating in the blood, are taken up by the reticuloendothelial cells of the corium and transformed into melanin under the action of light (ultraviolet) or oxidative ferments (dioxyphenylalaninoxydase)."

Tensile Strength of Hair.—CHENG (*Arch. f. Dermat. u. Syph.*, 1924, **147**, 550) finds from studies of the tensile strength of hair, that hair from which the fat has been removed is decidedly weakened and breaks more easily than hair which is oily or of normal fat content. He remarks upon the essentially unphysiologic character of many of the methods employed at present in dressing and treating the hair, in that they tend to produce a brittle, friable hair of low tensile strength.

Treatment of Chancroid.—REENSTIERNA (*Arch. f. Dermat. u. Syph.*, 1924, **147**, 362) reports the results of the treatment of 153 patients with chancroidal bubo (Ducrey infection) with an antistreptobacillus

serum obtained from rams and mixed with a sufficient amount of killed typhoid organisms to produce a febrile reaction. In cases in which the bubo had not been opened for drainage with resultant secondary infection, involution was accomplished in an average period of one week (five to ten days) which was one-fourth of the period required for a series of untreated chancroidal bubos to run their course. The chancroidal lesion itself is favorably influenced by this mode of treatment, but less by the antiserum alone. Two injections are given, separated by an interval of three to five days. A chill and febrile reaction with some local reaction at the site of injection and enlargement of regional lymph nodes follows the injection of the preparation, but no significant complications have occurred. In cases requiring further treatment of the chancroidal lesion, the application of heat, to which the Ducrey organism is especially susceptible, is recommended.

Kolmer Modification of the Wassermann Test.—Irvine and Stern (*Arch. Dermat. Syph.*, 1923, **8**, 818) present a valuable report of the results of the Kolmer modification of the Wassermann test in 5162 tests checked against the standard procedure of the laboratory of the Minnesota State Board of Health and against the clinical follow-ups of the cases. In 91.5 per cent there was agreement between the two tests. Of the 249 cases in which there was disagreement, 211 yielded positive Kolmer tests and negative routine tests. In this series in which the Kolmer proved itself to be more delicate than the routine only 3 cases occurred which did not have a history and clinical symptoms of syphilis. Of 43 cases in which the Kolmer test was positive and the routine test doubtful, only 2 had no clinical symptoms of syphilis. Of 108 tests which were doubtful only 1 failed to show clinical syphilis. Of 42 in which the Kolmer test was negative and the routine positive, the clinical follow-up indicated 11 cases of pulmonary tuberculosis, 13 cases of pregnancy with no symptoms of syphilis, 4 questionable diagnosis, 3 diagnosed syphilis, 2 cases of encephalitis, 1 case of Vincent's angina, 1 of eczema and 7 in which there were no symptoms of syphilis. The same type of findings indicated the greater reliability of the Kolmer test when the routine test was doubtful. In early syphilis the routine test gave 42 definite false positives as against a possible 5 for the Kolmer test. The Kolmer test yielded positive Wassermann reactions earlier in primary syphilis than did the routine test with an acetone insoluble antigen. Serum subjected to shipment or kept for varying periods showed more reliable results by the Kolmer than by the routine procedure and the Kolmer test could be trusted until the fourth day after drawing blood. It was found incidentally that there was less danger of wrong results from stale serum in syphilitic than in non-syphilitic processes. In the study of pregnant patients it was found that the Kolmer test showed little or no tendency to false positives, and yet did not miss true positive cases. The authors conclude that the Kolmer technic has many advantages over the ordinary Wassermann procedures, the only disadvantage being the larger amount of work involved and the delayed report due to the long ice-box incubation period.

OBSTETRICS

UNDER THE CHARGE OF

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Progress in the Relief of Sterility.—CURTIS (*Am. Jour. Obst.*, July, 1924) reviews the literature on the subject and also what has been accomplished in actual clinical work. He concludes if husband and wife give histories of good health, critical examination reveals no indication that a diagnosis of relative sterility is warranted only after the observation of three years. During this time the simplest treatment only is required. In but a very small percentage of cases is general ill health or improper diet or various physiologic disturbances the cause of sterility. Gonorrheal infection and infection following abortion are the most important and the most frequent causes. It is difficult to cure gonorrhea and very difficult to know when such a cure has been effected. The frequent practice of curettage is injurious because it tends to induce infection. Patients otherwise healthy are frequently found where sterility has followed the development of infection excited by curettage. Where there is no other pathology, the cure of abnormal conditions of the cervix is often followed by pregnancy. This is especially true where there is congenital obstruction of the canal or cervicitis with a purulent discharge. In contrast to this is the clinical fact that treatment of the body of the uterus has little influence in promoting conception. Where there is sterility with tubal disease, treatment—and by operation—gives much better results than formerly. Such cases should be very carefully selected and given appropriate treatment before operation.

When is Sterilization Indicated following Cesarean Section.—SWIFT (*Jour. Am. Med. Assn.*, July 19, 1924) considers this question in the light of his experiences in the Boston Lying-In Hospital. He reviews the histories of 95 patients who had repeated Cesarean section and exclusive of the original Cesarean section, 16 of his operations were done upon these patients. Fifty-seven of these 95 had a second Cesarean section; 21 had a second and third; 11 had a second, third and fourth; 2 had a second, third, fourth and fifth and 4 had a second, third, fourth, fifth and sixth. Among these patients were 4 deaths. Taking a large number of original Cesarean operations, in 850 cases, the mortality was 5.6 per cent. These were unselected and for all possible indications. This percentage is too high and does not represent the mortality at the present time when the operation is done under proper conditions and skilfully. The risk of a repeated Cesarean section is less than that of a primary section and the writer quotes cases illustrating this point. The convalescence after repeated section is more comfortable than with the primary operation. In the cases which he studied, there was no actual rupture of the old scar. Several of the scars showed definite weakness, but none ruptured. If such a patient is under close observa-

tion and the operation is done before or just as labor is commencing, the risk of rupture of the scar after Cesarean section is exceedingly slight. The writer believes that no patient should be sterilized without the written consent of both herself and her husband after they have thoroughly understood what sterilization entails. Each case presents a separate and different problem, but no woman should be sterilized in her first Cesarean section unless there are definite indications other than the possibility of a second Cesarean section. As successive operations increase, opinion tends toward suggesting and eventually urging sterilization. The writer believes that no patient should have more than 4 Cesarean operations. Methods of preventing conception from a medical standpoint are unreliable. It must be remembered that any Cesarean section carries more risk to the mother than delivery through the natural passage, but conditions may arise in which sterilization is justifiable. In discussion Holmes stated that in cardiac disease, chronic interstitial nephritis and tuberculosis complicating pregnancy, Cesarean section, when indicated, should include sterilization. Pelvic deformity is not an indication for sterilization. Where husband and wife request sterilization at a second Cesarean section, they must consider the fact that their children then living may die and the birth of other children will be impossible. They have, however, the right to insist that sterilization be performed. The danger of rupture of the scar is considerable and all women having had 1 operation should be in the hands of competent obstetricians during the second pregnancy. The question of State control of sterilization came up in discussion and it was believed that the decision in these cases should be left with the physician.

Morphin and Magnesium Sulphate as an Obstetrical Analgesic.—ADAMS (*Am. Jour. Obst.*, September, 1924) reports his results in the obstetrical and gynecological clinic of the University of Michigan. He used a 25 per cent solution of chemically pure magnesium sulphate, this was sterilized when required by boiling, it was then drawn into a sterile hypodermic syringe and the desired amount of morphin sulphate added. The injections were made into the deltoid muscle, the cases were not selected but were done as they entered the service. Sixty patients were so treated, 6 multiparæ and 54 primiparæ, the youngest fourteen and the oldest thirty-nine years, the average age was twenty, all were at term and all started labor spontaneously. Labor was slightly shorter than the average, there was no excessive postpartum bleeding, although one patient had a deep cervical tear. The uterus did not relax. Thirty-five of these cases had an ampoule of pituitrin after the delivery of the child, these patients had a greater blood loss than those who were not so treated. No bad results followed the treatment. Eighty-five per cent of the children cried spontaneously within one minute of birth; in 13 per cent there was slight cyanosis with normal heart beat; in 2 per cent there was pallid asphyxia and one child could not be resuscitated, autopsy revealed an enlarged thymus and a blood Wassermann of 4 plus. Comparing these with other cases where this method was not used, a very slight difference in favor of this method was observed with infants. Among these patients so treated 90 per cent delivered themselves, 8 per cent were delivered by forceps and in 1 case Cesarean section was done; the forceps were used for contracted

pelvis in 2, failure of rotation in 2, large child in 1. Comparing these with other patients, the use of forceps was a little less frequent, about 1 per cent in cases receiving the morphin and magnesium sulphate. At first the dose used was $1\frac{1}{2}$ cc of 25 per cent solution of magnesium sulphate and $\frac{1}{8}$ gr. morphin. This dose was ineffectual and 2 cc of the magnesium sulphate and $\frac{1}{6}$ gr. of morphin gave better results. The dose was repeated in 13 cases, 21.5 per cent. When this medicine was given the average dilatation was $4\frac{1}{2}$ cm. So far as the results are concerned in 93.4 per cent cases patients were more or less relieved by the treatment, in 6.6 per cent no results followed, 25 per cent had extremely easy labors with practically no pain until late in the second stage when ether was used. Ether was given in the last of the second stage in practically all the cases.

Fibroids in the Puerperal State.—FISCHMANN (*Surg., Gynec. and Obst.*, September 19, 1924) reviews the literature of the subject and reports the case of a primipara, aged forty years, large and well nourished with a large and symmetrical abdomen. On palpation two ovoids could be made out and but one heart sound. A roentgen-ray examination was requested, but refused. Labor began with rupture of the membranes and was tedious, finally terminating by the extraction of a male child weighing 8 pounds, $8\frac{3}{4}$ ounces, by the low application of the forceps. The uterus remained large and there seemed to be another fetal ovoid on the right side. On removing the placenta by the hand, the right side of the uterus was found to be occupied by a semisolid mass of unequal consistency. An hour and a half after delivery the patient had chills followed by fever which persisted for the next four weeks. The uterus remained large and there was a profuse and exceedingly foul discharge. The patient was placed in Fowler's position for drainage, ergot was given and iodin douches. About a month after delivery, following labor pains, there was a free discharge of pus with continued pain and on the following day the cervix was dilated by a mass which felt like a macerated fetal head. Under gas anesthesia this mass was finally delivered by Tarnier forceps. The uterus contracted, the fever subsided and the patient recovered. During her illness the blood cultures were sterile, the lochia showed many colon bacilli and staphylococci and there were colon bacilli in the urine. On examination the tumor was found to be fibroid more or less degenerated and necrotic and with localized suppuration. The degenerative changes were of about four or five weeks' duration. Opinions differ concerning the treatment of fibroids complicating pregnancy. The complete disappearance of the tumor after labor has been observed, but is rare. Some urge that no interference be practised unless the tumor is so situated as to render labor impossible. Others believe that operation should be performed at the beginning of labor in all cases. In the puerperal period, should symptoms of infection develop, hysterectomy should be done as soon as possible. Vaginal operations in these cases are often unsuccessful. Attention has been called to the danger of inversion of the uterus by spontaneous expulsion of a fibroid tumor after labor. In the experience of the reviewer a multiparous woman passed through a spontaneous confinement in the hands of a general practitioner without unusual symptoms. Her recovery was slow with attacks of pain and bearing-down. She visited several gynecological

clinics for relief. Several weeks after labor she was taken with pain and some discharge and her physician was summoned who found a mass on the perineum whose nature he did not recognize. He made traction upon this to deliver and succeeded in bringing it outside the vulva, when the patient had shock and great pain. He then desisted and called consultation, taking the patient at once to hospital. On examination a fibroid tumor had been expelled attached to the fundus of the uterus by a slender pedicle. Traction upon this pedicle had inverted the uterus. The tumor was readily removed and the uterus replaced, but the patient died of shock.

A Cervical Dilator for Use During Cesarean Section.—Dougal (*Jour. Obst. and Gynec., British Empire*, 1924, **31**, No. 2) has experienced, as have many others, difficulty in dilating the cervix in elective Cesarean section for the escape of blood from the uterine cavity. Drainage should always be secured after section, for retained blood in the uterus may set up after-pains and cause shock. It is sometimes possible to dilate the cervix from above through the uterine incision by the finger and some have passed a solid dilator from above, allowing it to enter the vagina from which it was subsequently extracted. The writer has devised a gutter-shaped dilator which he passes through the cervix from the uterine cavity, forming a channel through which blood can easily flow. It is $7\frac{1}{2}$ inches long by $\frac{5}{8}$ inch in diameter, and to introduce it a retractor is placed in the lower end of the uterine incision and the internal os dilated. The dilator is then inserted and pushed down until the upper end remains in the lower uterine segment; at the close of the operation the top of the dilator usually projects about $\frac{3}{4}$ of an inch from the vaginal orifice and can readily be removed. If it has lodged upon the perineum, it can also be readily extracted.

The Test of Renal Function in the Parturient Patient.—Lorenzetti (*Ann. d. Obstet. e Ginecol.* 1924, No. 9) has studied this question and concludes that the normal kidney function is not greatly disturbed in healthy pregnant women. The quantity of urine secreted has a tendency to lessen during the latter part of pregnancy and the puerperal period. A slight albuminuria during pregnancy is not uncommon and this may increase somewhat during the first days of the puerperal period. Primigravidæ are more susceptible to this than multigravidæ. In the presence of nephritis a genuine insufficiency of kidney function naturally develops. This may or may not be accompanied by eclamptic convulsions. Where the patient has had chronic nephritis, in the event of pregnancy and parturition there may be sudden kidney failure. Where pregnancy is complicated by heart disease or tuberculosis kidney function may suddenly and unexpectedly fail during labor or immediately after. The cause for this is more in the pathological condition present than in the pregnancy. Neither polyuria nor oliguria essentially influence the actual secretion of urine. Where the phthalein test is tried, its percentage does not always correspond with the quantity of albumin present or the number of casts. In a pregnancy complicated by renal lesions it may not be possible by the phthalein test only to modify the patient's condition by treatment, but the use of this test is of service in furnishing indications for treatment and in some cases for the interruption of pregnancy.

GYNECOLOGY

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End-results of Surgical Treatment in Cervical Cancer.—Reporting the work from Peterson's Clinic at the University of Michigan, CRON (*Wisconsin Med. Jour.*, 1924, **23**, 128) states that during the years from 1902 to 1920 there were 380 cases of cervical cancer admitted for diagnosis. They were clinically classified in two groups, either as early carcinoma when the lesion was localized to the cervix, or advanced where the involvement had extended to the vagina, bladder, rectum or outward to the parametrial regions, sacro-uterine ligaments or lymph glands. During this period of eighteen years only 60 cases were seen which could be classified as early cervical carcinoma. The remaining 320 were judged far advanced or at least inoperable from the standpoint of performing the radical Wertheim operation. During the early years zinc chlorid packs in and against the cervix was a favorite method of attack in the inoperable cases. Later excision of the cauliflower mass and curettage followed by cautery were favored, then cautery alone and finally Percy's much heralded technic of cauterization guiding the procedure by means of an assistant's hand in the abdomen. Since then the acetone treatment has been tried and more recently the roentgen-ray. Every patient excepting 1 eventually died directly or indirectly from the uterine malignancy. Of the 60 operable cases, 18 patients (40.9 per cent) are living and well five or more years after operation. When one considers, however, the end-results of all cases of cancer of the cervix seen in this series, it is found that only 5 per cent, or 19 out of 380 women, were cured. No wonder the great horror and fear women have of this disease. As a result of his study of this series the author comes to the conclusion that the life of women with advanced carcinoma of the cervix treated by packs or actual cautery is not materially lengthened, although the vaginal discharge and bleeding may be temporarily relieved. The percentage of cures in women with early carcinoma who survive the radical abdominal operation is favorable, but when one considers all the cases of cancer, the results from surgery alone are most discouraging. Deep roentgen-ray therapy by high voltage gives excellent palliative results and has replaced surgery in advanced cervical cancer; in fact radium and roentgen-ray should be used in all cervical cancer. Whether radium, roentgen-ray and surgery combined in early cancer will give better end-results than radium and roentgen-ray alone is still a disputed question which will only be decided after experience over a long period of time.

Plastic Restoration of the Tubal Canal.—There are occasional cases in which it may be advisable to restore the tubal connection to the uterus after previously having separated the tube from the uterus. STRASSMAN (*Zentralbl. f. Gynäk.*, 1924, **48**, 1681) presents two cases in which such a procedure was advisable and describes his technic in detail. In the first case a dermoid cyst adherent to the tube necessitated removal of the left tube and ovary, while on the right side there was a pregnancy in the interstitial portion of the tube, and not desiring to remove the entire tube, only the interstitial portion with the uterine cornu was removed. The remaining part of the tube was sutured into the opening in the cornu in such a manner that the end of the tube hung free in the uterine cavity. The fimbriated end was not disturbed. This patient expects to be married soon and has a great desire to have children. In the second case the patient had been married eight years but never had any children and at operation it was found that she had chronic pelvic inflammatory disease. The fimbriated end of the left tube was closed and a salpingostomy was done, although the author realized that the end-results of this operation are seldom favorable. On the right side the inflammatory disease was confined to the inner portion of the tube (salpingitis isthmica nodosa), the outer portion being patulous. The isthmus of the tube was removed and the outer portion implanted into the cornu of the uterus through a 2-cm. incision. Here again the anastomosis was made so that the end of the tube hung free in the uterine cavity. The uterine wall was closed over the tube with only one suture so that there would not be too much pressure on the tubal tissue. The operation is easily performed provided care is taken to ensure complete hemostasis, and thus avoid a hematoma and breaking-down of the wound. The technic is very similar to the implantation of the ureter into the bladder. The operation is only advisable when the opposite tube is not patulous and should never be done when the other tube is normal. Furthermore, the part of the tube to be implanted must be patulous to a sound and apparently healthy. In fact, by threading the tube over a sound it is easily held in place while the anastomosis is made and the uterine wound sutured. It should also be remembered that the operation should only be done when the woman desires children and is in a proper physical condition to bear them. A case in which an operation of this type was followed by pregnancy was reported from Cullen's clinic a few years ago.

Primary Carcinoma of Urethra.—There have been only 99 authentic cases of primary carcinoma of the female urethra reported in the literature, and in adding one case to this list, O'CONOR (*Jour. Urol.*, 1924, **12**, 159) describes a very extensive urethral carcinoma which was locally destroyed with subsequent complete healing of the urethral and vulvar regions by means of diathermy. Complete urinary function was retained and local symptoms were completely relieved by the procedure. He is quite enthusiastic over the result and suggests that diathermy offers a method which is superior to any previously described in effecting the local destruction of carcinoma of the female urethra. This is especially true if we bear in mind the minimization of metas-

tases by the complete sealing off of the surrounding tissues during the slow coagulation. The procedure is devoid of operative shock, a general anesthetic is unnecessary, postoperative discomfort is slight and even in advanced cases urinary control can be maintained. The treatments which have been tried heretofore for this distressing condition make us hope that diathermy will do in similar cases what it apparently has done in this particular case of the author.

Childbearing after Radiation.—PEMBERTON (*Surg., Gynec. and Obst.* 1924, **39**, 207) has been questioned so many times by physicians in regard to the danger of causing poorly developed, deformed or backward children or even sterility in fertile women by the use of radium for therapeutic purposes that he believes that the known results are not common knowledge and therefore he discourses upon the subject. He reminds us that the result of radiation in the ovary is well established by the examination of animal and human ovaries after treatment. The maturing Graafian follicles are more susceptible to radiation than the primordial follicles, which is very important, as will be seen. In a well developed follicle the changes consist in a degeneration and destruction of the ovum and membrana granulosa, preventing the follicle from going on to maturity and leaving a small cyst. In less advanced follicles the ovum is destroyed but the single layer of granulosa cells is preserved. If a dose has not been large enough to cause a menopause, however, the primordial follicles remain intact, capable of maturing normally. Theoretically then, it is possible to use such a dose of radiation that mature follicles may be destroyed but primordial follicles not damaged. This is what seems to occur clinically. Following treatment the patient may menstruate normally, have a scanty flow, or amenorrhea for a few months depending on the size of the dose. If amenorrhea occurs with this small dosage it is followed by a reëstablishment of menstruation except in rare unusually susceptible cases. Ovulation and menstruation are believed to be definitely related to each other. Therefore theoretically if menstruation is present, fertility is possible. The other important consideration is the possibility of the fertilization of a partially damaged ovum. Theoretically this might result in a deformed or poorly developed child or a so-called blighted ovum. There appears to be no data in regard to this point. The percentages of miscarriages is greater in radiated than in normal mothers, but no one has reported the birth of a deformed child and only a few underdeveloped ones are found. At the Free Hospital for Women, Pemberton reviewed reports obtained from 25 married women in the childbearing age who had been treated with radium inside the uterus for uterine bleeding. Their average age was thirty-four years. Four of them reported pregnancy after the treatment, 2 of them going to full term, 1 had a premature labor at seven and a half months due to eclampsia and the other miscarried at the third month. Therefore, Pemberton states that it is evident that a patient can be treated with radium and bear normal children subsequently. He has no data on whether or not such treatment decreases the chance of becoming pregnant in women who wish children and it would be difficult to get reliable information. It is probably true that deformed or underdeveloped children are not likely to follow such treatment. A damaged ovum is not capable of

being fertilized, or if it is, it probably results in a blighted ovum which comes away by miscarriage. It is important to examine the products resulting from such miscarriages to find out if the fetus is absent or deformed. Care should be taken not to treat pregnant women, because it may cause interference with the growth of the fetus.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Effect of Thyroxin on the Cutaneous System in the Sheep.—Simpson (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 572) observed that, following the administration of thyroxin to an eight-months-old, thyroidectomized lamb, the fleece began to fall out until, in the course of twenty-days, the whole animal was bare to the skin, save for the head and neck. The thyroxin was given, originally, in doses of 0.5 mg. to save the animal's life. As the lamb improved, the dose was diminished to 0.25 mg. and then to 0.125 mg. The shedding of the wool began about one month after the initial dose of thyroxin. Two normal sheep were then inoculated with thyroxin. One sheep showed no effect while the other, in about a month, reacted as the thyroidectomized lamb had done, only to a lesser degree.

Production of Goiter in Rats by Restricted Iodin Feeding.—Hayden, Wenner and Rucker (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 546) divided two litters of white rats, half of each being placed in a separate cage. All the rats were fed a diet consisting of 53 parts oats, 25 parts patent flour, 20 parts linseed meal, 1 part calcium phosphate and 1 part sodium chlorid. One group was given distilled water to drink, and the other, water containing 0.1 mg. of iodin per liter. Two rats on each diet were killed after four weeks and the thyroids weighed. This procedure was repeated every two weeks until all had been killed. It was found that the thyroids in those rats not receiving iodin were twice as large as they were in the other group.

The Effect of Anesthesia and of Sedatives on the Serum Therapy of Experimental Botulism.—The rapid progress of the intoxication in severe cases of *botulinus* poisoning in man has rendered of questionable value the therapeutic use of antitoxin in such instances. In the course of a series of experiments designed to investigate the path of absorption of *botulinus* toxin, Bronfenbrenner and Weiss (*Jour. Exper. Med.*, 1924, **39**, 517) observed that guinea-pigs under ether anesthesia remained alive for hours after the death of unanesthetized guinea-pigs that had

received a similar amount of toxin. Because of the importance attached to any method delaying the intoxication in botulism, the authors investigated the influence of ether and other drugs minutely. It was found that when guinea-pigs were fed large quantities of *botulinus* toxin they developed symptoms of intoxication within six hours and usually died within twelve hours after the feeding of toxin. And, if very large amounts of toxin were introduced intraperitoneally, the animals died, as a rule, within two hours. If, however, the guinea-pigs were etherized, their life was prolonged by a period approximately equal to that during which the administration of the anesthetic was continued. The giving of the ether delayed the progress of intoxication but did not alter the toxin or the nature of the mechanism of intoxication—not only when administered immediately after the intake of toxin but when administered much later, after the intoxication had progressed far enough to cause definite objective symptoms of poisoning. Similar results were obtained with luminal sodium, nitrous oxide—oxygen mixture and morphin. The authors conclude by saying that "in view of the fact that the published data indicate that *botulinus* antitoxin has thus far failed to give beneficial results in the treatment of botulism in human beings because, as it would seem, of the rapid progress of intoxication, any method of delaying the progress of intoxication to supplement the antitoxin therapy deserves consideration."

The Biological Action of the Beta Rays of Radium.—"Methods of radium therapy commonly employed consist in the application of the radium over the surface of the area to be treated or in the insertion into the tissue to be influenced of metal needles containing radium. In both instances the radium rays are filtered in such a manner that only the gamma rays penetrate into the tissues and act as a therapeutic agent." By collecting radium emanation in capillary glass tubes from 1 to 5 mm. long and 0.25 mm. in diameter and inserting these tubes into such structures as normal liver, spleen and bone marrow of rabbits, muscles and testicles of rats and mice, sarcoma of rats, carcinoma of mice, young plant tissue, crown galls of geranium and club roots of cabbage, LEVIN (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 462), working in coöperation with Michael Levine, was able to make a gross and microscopical analysis of the irradiated tissues to determine the effect of both the beta and gamma rays. It was found that the zone of tissue immediately surrounding the glass capillary was in a state of complete necrosis. The second zone showed characteristic gamma-ray irradiation changes in the protoplasm and nuclei of the cells. This latter zone was more extensive in tumor than in normal tissues. In addition, tissues obtained on clinical material were studied at various intervals after the insertion of the glass capillaries. Not only were the clinical results very significant but pathological conditions, which did not yield to large quantities of filtered rays, responded readily to beta-ray action. The author indicates that the beta-ray action is not a caustic one, but is qualitatively analogous to the action of the gamma rays. After a discourse of the present-day conception of the physics of the various rays, he says that "the biological action of the gamma and beta must be analogous." "The difference is quantitative and is due to the fact that the ratio of beta and gamma rays in a unit of radium is about

100 to 1. Five millicuries of radium emanation distributed to 10 capillaries will destroy 10 cm. of carcinoma. To produce the same effect by surface application the gamma rays of 500 mc. would have to be employed. The statement made by physicists that the biological effect of 1 mc. of radium emanation buried in the tissues equals 132 mc. hours of surface application of filtered radium must be corrected since it does not take into account the action of the beta rays and their secondary roentgen-rays."

Observations on Some Causes of Gall-stone Formation. I. Experimental Cholelithiasis in the Absence of Stasis, Infection, and Gall-bladder Influences.—Rous, McMaster and Drury (*Jour. Exper. Med.*, 1924, **39**, 77), in reporting their observations on lithiasis developing in dogs permanently intubated for the collection of sterile bile, as described by Rous and McMaster (*Jour. Exper. Med.*, 1923, **37**, 11), say "whatever the significance of our findings, or lack thereof, there can be no doubt that the problem of cholelithiasis waits upon the development of an experimental material." The literature of the subject has been "from early times a literature top-heavy with hypothesis and dismal with uncorrelated observations." Gall stones developed in 14 out of 22 intubated dogs. The stones were formed from liver bile. Thirteen of the animals were kept with special reference to maintenance of health, and in 7 of these calculi developed. Four of this number had daily sterile cultures of bile. The secretion had become infected in 4 of the 6 animals which did not show stones at autopsy. "Nine intubated dogs were submitted to procedures that may have, and often undoubtedly did, produce pathological changes in the secretion, as for example, the intravenous injection of hemoglobin or calcium chlorid, prolonged chloroform anesthesia, and toluylenediamin poisoning. Seven of these developed calculi. The bile was infected in only 2 of these 7 instances of lithiasis and in 1 of the 2 dogs that were free from stones. The stones always occurred in the system of glass and rubber tubes which connected with the common duct and developed as early as fourteen days after intubation. In general the stones exhibited little variety of structure and composition as compared with human stones. three general types of stones could be discriminated, one consisting almost wholly of calcium bilirubinate, another of calcium carbonate, and a mixed type in which both compounds were present. The stones were found not to be the result of bile loss." In a companion essay, Rous, Drury and McMaster (*Jour. Exper. Med.*, 1924, **39**, 97) reported the results of a study of the early history of the gall stones with special reference to the role of preformed nuclei in their development. Utilizing the same material, the authors found that only very occasionally did the calculi form in the absence of a special center of deposition. Sometimes a particle of talc from the wall of the rubber collecting tube served as a nucleus, but more often the calculus formed in the midst of small masses of organic débris, or deposition of the salt occurred upon the surface of bilirubinate calculi. After reviewing at some length the factors concerned in the genesis of gall stones consisting of calcium carbonate, the authors believe that their evidence supports the view that the development of carbonate stones in human beings as well as in the dog may be a consequence, not of changes in the bile

brought about by microörganisms, nor of the elaboration of an inflammatory exudate rich in calcium salts, but merely of inflammation such as leads to lessened motility of the duct system with the accumulation of organic débris. "The fact that infection is almost the sole agent whereby such inflammation is set up and maintained in clinical instances has led too often to the conclusion that it serves as the essential agent in the process of calcification." Continuing their detailed observations on some causes for gall-stone formation, DRURY, MCMASTER and ROUS (*Jour. Exper. Med.*, 1924, **39**, 403) reported certain experimental findings having to do with the relation of the reaction of the bile to experimental cholelithiasis—or, as they aptly put it "with the reasons for the absence of such stones from dogs with an intact biliary tract." There are several evident safeguards against stone formation within the ducts, as they have suggested, "their motility, the cleansing and possibly antagonistic action of the secretion they themselves elaborate, and the flushing out effected by an intermittently quickened bile stream." "But how is one to explain the absence of calculi from the gall-bladder, a viscus which, according to the latest evidence, empties itself but poorly, and in which the bile often undergoes great concentration and must frequently be held for many hours together." "In view of the marked tendency for calcium carbonate to come down out of liver bile on standing, and for it to deposit within old organic débris, it seems certain that the normal gall-bladder must either effect some change in the secretion in the direction of safety, or else add some preventative against deposition." The solubility of calcium carbonate is known to be markedly affected by the reaction of the fluid in which it is contained. The normal liver bile, out of which it tends to precipitate, is alkaline, with an average pH of 8.20 but in the gall-bladder where conditions might otherwise seem especially favorable to precipitation, the secretion undergoes a change toward the acid side, becoming on long sojourn there, strongly acid to litmus (pH 5.18 to 6.00). From bile thus altered, no carbonate precipitation occurs, even when it becomes greatly concentrated as in fasting animals or after obstruction of the common duct. The authors conclude by stating that "the possibility that cholelithiasis may be a consequence of sins of omission on the part of the biliary channels and reservoir deserves to be considered."

Seasonal Changes in Organ Weights and their Relation to Meteorological Conditions.—"It is well known that many of the endocrine glands of normal animals undergo rhythmic changes in weight per unit of body weight which conform, in general, with seasonal conditions." Since the cause of these changes is not clearly understood, BROWN, PEARCE and VAN ALLEN (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 373) studied the ratio of the weights of various organs and tissues to the body weight of normal rabbits and the limits of variation which might be encountered. The factors studied included age, breed, length of caging, time of killing (with reference to the regular system of feeding), and meteorological conditions. All the animals were males and were fed on a uniform diet of hay, oats and cabbage. Two groups of rabbits selected from stocks that were being used for experimental work, were killed each month and the various organs were weighed. The weights were then reduced to terms per unit of net body weight which was

determined by subtracting the weight of the gastro-intestinal mass from the live weight of the animal with additional allowance made for excess urine in the bladder. All the organs examined were found to undergo rhythmic changes in weight per unit of net body weight which conformed, in general, to the progression of the seasons. In the case of organs such as the heart, kidneys and liver, the transition from one condition to another occurred relatively slowly (20 to 40 per cent), and the maximum variation in any direction was distinctly less than that noted in the case of a number of the endocrine glands and the lymphoid tissue (50 to 100 per cent). On attempting to correlate this series of seasonal variations in organ weights with meteorological conditions, it was found that the majority of them corresponded in time and direction with prevailing conditions of sunlight. In general, the periods of maximum and minimum weights coincided with high or low levels of daily sunlight while the change in direction and the transition from one condition to the other corresponded with the change in sunlight from winter to summer or from summer to winter. It appeared that the weight curves of some organs conformed more closely to the curve of temperature or to humidity than to the curve of sunshine, and that the degree of correlation in any case was subject to the influence of other factors. The authors were able to deduce from their observations that no fixed relationships exist between the various organs and tissues of the body—that mass relationships and probably functional activities are subject to continuous change in response to certain external influences such as are represented by climate or meteorological conditions; that these changes tend to pursue a rhythmic course in harmony with the progression of the seasons, but that they are retarded or accelerated or otherwise affected in accordance with the prevailing meteorological conditions; and that, in considering the influence of factors of this kind, there are two things to be taken into account, namely, the normal or prevailing level of activity and the factor of change.

HYGIENE AND PUBLIC HEALTH

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Observations on the Presence of a Toxic Substance in the Blood and Urine of Patients with Scarlet Fever.—TRASK and BLAKE (*Jour. Exper. Med.*, 1924, **40**, 381) state that a series of observations on the blood of patients acutely ill with scarlet fever has shown that a toxic

substance can be demonstrated in the serum by means of intracutaneous injections of the serum in persons who have not had scarlet fever and whose serums fail to blanch the rash in scarlet fever. The reaction caused by this substance consists of a bright red local erythema, varying from 20 to 70 mm. in diameter, of one to four days' duration. The severer reactions are moderately indurated and tender and are followed by pigmentation and desquamation. Control injections in persons whose serums blanch the rash in scarlet fever cause no reaction. The toxic substance is not neutralized by mixture with a human serum which gives a negative blanching test but is readily neutralized by a human serum which gives a positive blanching test. It is not neutralized by normal horse serum but is completely neutralized by Dochez's scarlatinal antistreptococcic serum. In a limited number of observations on the urine of patients with scarlet fever a similar toxic substance has been found in 2 out of 5 cases studied. Since the toxic substance described appears to resemble the toxic substance found in the filtrates of scarlatinal hemolytic streptococcus cultures by Dick and Dick, and since it is neutralized not only by a blanching human serum but also by Dochez's scarlatinal antistreptococcic horse serum, the experiments reported support the conception that scarlet fever is a local infection of the throat by a particular type of Streptococcus hemolyticus capable of producing a toxin which is absorbed and is the cause of the general manifestations of the disease.

Inflammatory Reaction of the Immune Animal to Antigen (Arthus Phenomenon) and Its Relation to Antibodies.—Opie (*Jour. Immunol.*, 1924, **9**, 231) says that local anaphylaxis or the Arthus phenomenon is an inflammatory reaction which occurs when an animal immunized against a protein is reinjected with the same antigen; it is caused by an antibody present in the blood serum and tissues of the immunized animal and occurs when antigen and antibody meet in the tissues. This reaction which varies in intensity in different species of animals, and may fail to occur in some (rat, dog), bears a close but not exact relation to the ability of the animal to form precipitin. An animal passively immunized by injection of serum of an immunized animal exhibits the reaction which may be so severe that necrosis occurs. Simultaneous injection of antigen and of serum from an immunized animal causes acute inflammation at the site of injection. In animals with either active or passive immunization there is a very close but not exact parallel between precipitin content of the serum and the occurrence and severity of specific inflammation. The discrepancies observed do not exclude the possibility that precipitin is the antibody concerned.

Immunological Studies in Tuberculosis: II. Further Observations on Skin Hypersensitiveness in Experimental Tuberculosis.—Petroff (*Jour. Immunol.*, 1924, **9**, 309) says that true tuberculin skin hypersensitiveness can be set up in a normal animal by the injections of tubercle bacilli killed at 100° C. for one hour. From unpublished work he has further proof that the substances responsible for setting up true hypersensitiveness are not even destroyed by heating for a half hour at steam pressure at one atmosphere (121° C.). The success

of this sensitization depends on the following few points: The tubercle bacilli must be triturated well, made up in good suspension, and the reaction adjusted to pH 6.9 or 7.0 before sterilization. Above all, one of the most important points is that animals suitable for such sensitization must weight 400 gm. or over. They must be well fed and kept in good condition. The injection should be made every three or four days. It seems, so far, that the intraperitoneal route is the most suitable one. After each injection of killed tubercle bacilli there is a distinct drop in the weight of the animal. In a day or so the animal again picks up his weight, but the drop follows after subsequent injections, and as soon as the three injections have been made, the animal gradually recovers the loss and begins to gain very rapidly. It is an interesting observation that if the animal suddenly begins to lose weight the skin hypersensitiveness also diminishes somewhat.

Microbic Virulence and Host Susceptibility in Paratyphoid-enteritidis Infection of White Mice: V. The Effect of Diet on Host Resistance.—WEBSTER and PRITCHETT (*Jour. Exper. Med.*, 1924, **40**, 397) found that white mice from the Rockefeller Institute breeding-room fed on a McCollum complete diet, consisting of whole wheat (67.5 per cent), casein (15 per cent), milk powder (10 per cent), NaCl (1 per cent), $CaCO_3$ (1.5 per cent) and butter fat (5 per cent) are more resistant to mouse typhoid infection, mercury bichlorid intoxication, and botulinus toxin than are similar mice fed on bread and pasteurized milk supplemented by an oatmeal and buckwheat mixture and dog biscuit.

A Histological Study of the Central Nervous System in Experimental Botulinus Poisoning.—COWDRY and NICHOLSON (*Jour. Exper. Med.*, 1924, **39**, 827) says that the results of their observations indicate that, except for a slight degree of vascular engorgement, all the lesions which they have noted in the brains of mice, guinea-pigs and rabbits suffering from botulinus poisoning are readily susceptible of some explanation other than that they are produced by the direct action of the toxin upon the central nervous system. This absence of microscopical evidence of a central action of the toxin is not, of course, conclusive proof that the cells in the brain are not primarily involved, because it is quite conceivable that, owing to the delicacy of the nervous mechanism, the toxin might well act centrally without leaving any traces microscopically visible. But the observations do not tend to show that, upon the histological side, there is no evidence inconsistent with the results of physiological experiments indicating that the site of action of the toxin is upon peripheral nerve terminals.

Transmission of a Flagellate Infection from Plant to Animals.—STRONG (*Am. Jour. Hyg.*, 1924, **4**, 345) has shown that a flagellate which produces a disease in plants (Euphorbiæ) may be passed through an invertebrate, the lizard (Cnemidophorus lemniscatus). An insect (Chariesterus cuspidatus) transmits the infection from the plant to the lizard. From the invertebrate host it was transmitted to a monkey, in which it gave rise to a form of tropical ulceration in the skin. In this ulceration the leishmania form of the parasite and not the flagellate stage is encountered. This is the first time a chain of infection due to

a parasite primarily producing a disease in plants has been shown to pass through an invertebrate to a vertebrate host and acquire pathogenic properties for mammal. We here see the evolution of disease in the making.

The Relation of Vegetative Activity of Bacteria to Pathogenicity.—FELTY and BLOOMFIELD (*Jour. Exp. Med.*, 1924, **40**, 703) report experiments showing that distinct differences exist between relatively young cultures of bacteria and the same strains during the period of decline as regards invasive power and pathogenicity, and that these differences must be distinguished clearly from specific alterations in virulence such as those produced by animal passage. The exact interpretation of these observations is not, however, perfectly clear. The authors are inclined to believe that simple alterations in vegetative activity might account for the differences which have been described, but to what extent the results have been due to injury to the bacteria by products of culture growth it is impossible to say, and further work will be necessary to settle this point. At any rate the experiments seem to bear definitely on the problem of infection in as far as they show that purely temporary modifications of growth activity, whether or not brought about by specific injury, lead to changes in invasiveness which are quite analogous to the test-tube phenomenon of lag. The authors have previously shown that there exists in the upper air passages a mechanism by means of which foreign particles and bacteria can be eliminated within a few hours. They state that it seems highly likely on the basis of their present work that bacteria entering in an inactive growth phase—for example dried in dust or perhaps from a chronic carrier—may be disposed of before activity can be resumed, whereas organisms introduced in the stage of active growth—as from a case of acute disease—may be able to take advantage of a portal of entry. It is further possible that these experiments may have some bearing on the genesis of epidemics, especially as regards the preëpidemic phase, and these matters will be discussed at another time.

Outbreaks of Botulism at Albany, Oregon, and Sterling, Colorado February, 1924.—STRICKER and GEIGER (*Pub. Health Rep.*, 1924, **39**, 655) report that in the first outbreak 12 persons were affected and 8 of these died. It was found that home-canned string beans were responsible, and the interesting fact was brought out that not all the food which was toxic was obviously spoiled. The incubations period was from 16 to 40 hours and death occurred in from 27 to 103 hours. In the second instance there were 7 cases, with 5 deaths. Home-canned string beans were responsible for this outbreak also.

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